AUTHORS' REPLY We are grateful to Dr Meeran for his comments on this patient. He will be aware that since the introduction of multichannel automated analysis of serum it has become clear that asymptomatic patients with biochemical primary hyperparathyroidism are not uncommon.[1] This patient clearly fell into this category and had no evidence of active bone disease. Furthermore, the changes in his urinary hydroxyproline: creatinine ratio and alkaline phosphatase activity during four weeks' treatment with prednisolone 20 mg daily were almost identical to those of the other nine subjects studied in timing and degree.

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Lymphocyte and lymphocyte subset numbers in blood and bronchoalveolar lavage and pleural fluid in various forms of human pulmonary tuberculosis

The study by Dr G M Ainslie and others (July 1992;47:513–8) is an important contribution to the understanding of the factors determining the course of tuberculosis. The authors observed that the CD4:CD8 lymphocyte ratio is lower in bronchoalveolar lavage fluid from patients with tuberculosis, particularly the miliary form, than from control subjects. These results complement those of our immunocytochemical studies on biopsy material from the tuberculin reactions of BCG vaccinated subjects, which had two principal cellular components[1]: a focal perivascular collection of blood derived white cells, the CD4:CD8 ratio of which mirrored that of the blood, and a diffuse infiltration of some of these cells into the intervening dermis with a preferential migration of CD4 cells. Although the CD4:CD8 ratio in the diffuse infiltrate was always higher than that in the blood, this ratio was considerably lower in patients with tuberculosis than in healthy individuals. If similar selective mechanisms occur in the inflammatory lesions of tuberculosis, the CD4 infiltrate would be reduced with an impairment of the immune defences. It would be interesting to determine whether the CD4:CD8 ratio in the cellular content of the diffuse dermal infiltrate in the tuberculin reaction correlates with that in the pulmonary lesions or lavage fluid.

These cytometric studies support the concept of an immunological spectrum of tuberculosis and reveal similarities to the spectrum of leprosy, in which reactive lesions contain many T cells, mostly CD4, and anergic lesions contain fewer T cells, mostly CD8.[2,3] Thus the manifestations of mycobacterial disease in the individual patient may be determined, at least in part, by the number and ratio of T cell subsets in the lesions. In addition, any therapeutic intervention that rectifies the defects should restore immunocompetence in both diseases.

The injection of small amounts of interferon gamma into lepromatous lesions leads to a rapid infiltration of lymphocytes, an increase in the CD4:CD8 ratio to around 1·0, and an enhancement of granuloma formation.[2] The effects of systemically administered interferon gamma and other cytokines in mycobacterial disease would, however, probably be non-specific and might enhance tissue destroying hypersensitivity reactions.

There is, however, increasing evidence that the intradermal injection of a suspension of autoclaved *Mycobacterium vaccae* corrects inappropriate immune reactivity in tuberculosis at a more fundamental level by suppressing tissue destroying immune reactions and restoring protective ones.[4] It would be exciting to determine the nature of the changes in the cellularity of the lavage fluid or tuberculous lesions of patients given such immunotherapy and to see whether it reverses the CD4 lymphopenia that occurs in the blood of patients with tuberculosis, as shown by Dr Ainslie and colleagues, especially in those whose CD4 cells are already compromised by HIV infection. Further information on the regulation of immunological phenomena occurring in tuberculosis is desperately needed because it is increasingly obvious that only a greatly shortened therapeutic regimen, with immunotherapy as a key element, can reverse the alarming increase in the global incidence of tuberculosis.[4]

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26 1 *Beck JS, Morley SM, Lowe JG, Brown RA, Grange JM, Gibbs JH, et al.* Diversity of migration of CD4 and CD8 lymphocytes in different microanatomical compartments of the skin in the tuberculin reaction in man. *Br J Exp Pathol* 1988;69:771–80.
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AUTHORS' REPLY We thank Dr Grange and others for their response to our paper and for drawing attention to the similarity of our findings in bronchoalveolar lavage fluid in tuberculosis and theirs in skin biopsy material from tuberculin positive BCG vaccinated subjects. They suggest that our findings support the concept of an immunological spectrum in tuberculosis similar to that found in leprosy. We believe that they have misinterpreted our results, and suggest that the concept of a spectrum in tuberculosis is an oversimplification and cannot accommodate the wide range of immunological phenomena found in different organs, even within a single patient and over time. This is not surprising considering the greater pathogenicity of *Mycobacterium* tuberculosis (compared with the more limited invasiveness of *M leprae*).

The findings in our study that argue against a spectrum such as is found in leprosy include the following. The reduced CD4:8 ratio in the lavage fluid from patients with miliary tuberculosis before treatment was most pronounced in those with the greatest increase in lymphocyte numbers, and thus represented an absolute increase in CD8 cells. The low CD4:8 ratio was therefore not the result of CD4 lymphocyte depletion, as suggested in their letter. Furthermore, recovery was slower rather than faster in patients with increased lavage lymphocyte numbers. Secondly, the skin reactivity to purified protein derivative (PPD) of patients in our study (results not published in the current paper) is at variance with the "spectrum" hypothesis. Thirty eight per cent of patients with miliary tuberculosis in our study had a positive reaction (>10 mm induration) to 5 TU of intradermally administered PPD at 48–72 hours. The lymphocyte findings in blood and in lavage fluid in PPD positive and negative patients are compared in the table below. Although PPD responders tended to have higher total lymphocyte numbers in blood and lavage fluid, the only significant difference was a lower (not a higher) number of CD4 lymphocytes in responders (with correspondingly lower CD4:8 ratios).

Thirdly, we would draw attention to the fact that lymphocyte response may vary in the different organ "compartments." For example, in one patient in our series the pleural fluid showed a characteristic exuberant CD4 response, whereas blood and lavage fluid showed increased numbers of CD8 lymphocytes. Possibly simultaneous sampling of that patient's tuberculin skin reaction would have yielded a CD4 response.

Thus it is better to consider separately the responses in different anatomical locations than to attempt to define immunological reactivity in tuberculosis along a bipolar scale. In our study blood and lavage fluid responses were similar but responses in the pleura were different. We do, however, support the suggestion that these differing responses in different locations have a bearing on the outcome of infection and the tissue destruction that ensues, and that the current attempts to

Comparison of mean (SD) lymphocyte and lymphocyte subset numbers in peripheral blood and lavage fluid in Mantoux positive and negative patients with miliary tuberculosis before treatment

	Mantoux test reaction		
	Positive (n=6)	*Negative (n=10)*	*p**
Peripheral blood			
Total lymphocytes ($\times 10^9$/l)	1·9	1·6	NS
CD4 (%)	57·8 (6·2)	69·4 (9·7)	<0·05
CD4:8	1·42 (0·3)	2·64 (1·4)	<0·1
Lavage fluid			
Total lymphocytes ($\times 10^3$/ml)	87	35	NS
CD4 (%)	43·6 (6·3)	54·6 (9·1)	NS
CD4:8	0·89 (0·2)	1·3 (0·6)	NS

*Fisher's exact test.