

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 components¹: 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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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 find-

ings 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		p*
	Positive (n = 6)	Negative (n = 10)	
Peripheral blood			
Total lymphocytes (x 10 ⁶ /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 (x 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.

modulate components of the immune response, particularly those causing tissue destruction, are important and should be pursued.

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Variability of inspired oxygen concentration with nasal cannulas

The paper by Dr EA Bazuaye and others (August 1992;47:609-11) on inspired oxygen concentrations from nasal cannulas ("prongs") is welcome. The potential hazards of nasal oxygen are underappreciated, as we found when asking junior medical staff how they use oxygen during exacerbations of chronic ventilatory failure.¹ This inquiry followed a particularly spectacular example of "prong poisoning," where nasal oxygen at 1 litre per minute delivered an F_{IO_2} conservatively estimated at 40%.¹ Nearly half the doctors we asked thought nasal oxygen was as good as or better than a Venturi mask in these circumstances, and only one appreciated that nasal cannulas deliver an F_{IO_2} which can rise as respiratory failure worsens and ventilation falls. Our case supports the suggestion of Dr Bazuaye and colleagues that nasal cannulas may be more hazardous during acute exacerbations of ventilatory failure, and sustains their statement that nasal cannulas are "unsatisfactory if precise control of inspired oxygen is desired."

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Randomised clinical trial of chest drainage systems

We should like to comment on the article by Dr ANJ Graham and others (June 1992;47:461-2). The study sample consisted of only postoperative cases, though the authors have extended the recommendation of a Portex drain to trauma and emergencies where the risk of tube blockage is higher and low pressure negative suction is invariably required.¹ In selecting their sample the authors have excluded patients who would require suction, but in the discussion they have analysed the requirement of suction in two groups. This would be a major confounding factor in the study. The reasons for reduction in "time to sitting" and in morbidity with a Portex drain, although drainage with bottles was adequate, are not discussed. As the drainage systems were not "blind" and there was variable encouragement for mobilisation by the nursing staff, there is scope for a bias for mobilisation of the two study groups and thus in the observations. The major factors in the early mobility of patients and discharge would be the type of underlying and associated illness and complications. Con-

sidering the requirement of suction and the possibility that Portex tubes can fall out, the authors' recommendations need further evaluation.

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AUTHORS' REPLY We thank Dr Sarniak for showing interest in our paper. His assertion that chest drains inserted after thoracic trauma invariably require suction is not, in fact, supported by the reference he cites. In our experience this is necessary only in cases of persistent pneumothorax, usually because of a massive air leak.¹ Pleural suction is not readily available at the roadside or battlefield and the advantages that drainage bags have over underwater seals in these circumstances are obvious. This is supported by recent military experience in wartime conditions.²

Patients were not entered into the trial if it was known that postoperative pleural suction would be essential. Randomised patients who subsequently required suction were retained in the study and the results were analysed according to the intended treatment. This is an accepted method for reducing bias in this type of clinical trial.³

There are inherent difficulties in carrying out a trial comparing such different methods of treatment. It was not possible to perform a blind study. Nevertheless, we believe that it is important to attempt to assess different techniques in a randomised fashion rather than basing management on uninformed opinion and speculation. The fact that drainage bags were found to be safe when used after elective surgery, which is in effect a form of thoracic trauma, should give clinicians the confidence to use them, when required, in emergency conditions.

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Barcelona's asthma epidemics

With regard to Dr C Picado's "For Discussion" paper (March 1992;47:197-200), we propose that exogenous 15-lipoxygenase enzyme from soybean modulates the severity of the asthma response in soybean induced asthma, since soybean is the world's richest known source of lipoxygenase enzyme and is causal in epidemic asthma with the unusual clinical features described by Dr Picado.

Plant lipoxygenases are common in nature and could readily be aerosolised during the bulk handling of dry soybean. After antigen challenge a product of the 15-lipoxygenase

pathway of arachidonic acid metabolism—namely, 15(S)-hydroxy-5,8,11-*cis*-13-*trans*-eicosatetraenoic acid (15-HETE)—is observed in large amounts in bronchoalveolar lavage fluid from patients with chronic stable asthma. Eosinophil suspensions incubated with ionophore and granulocytes when stimulated in the presence of 15-HETE produce lipoxin A_4 .¹ A characteristic of asthma is the presence of eosinophils in bronchial exudates. Lee *et al* have found lipoxin A_4 in the bronchoalveolar lavage fluid in human pulmonary disease.² Lipoxin A_4 elicits constriction of the guinea pig lung strip, is chemotactic and chemokinetic in response to leucocytes, and may further regulate arachidonic acid release. Lai *et al* showed that preinhalation of 15-HETE increased the early asthma response in atopic individuals by 39%, with no late response, after stimulation by antigen.³ It is therefore likely that the exacerbation of the asthmatic response seen after the inhalation of soybean dust is due to the excessive production of lipoxins or related products. We submit that the magnitude of that response is due to the exogenous enzyme. The clinical features in the Barcelona epidemics that support this hypothesis are: sudden onset, severity, and rapid recovery; augmentation of the early asthma response and no late phase response; and a lack of clinical reproducibility with standard methods of antigen challenge.

Dr Picado's paper provides the clinical observations necessary to describe a novel human disease mechanism whereby exogenous lipoxygenase enzymes may gain access to human substrates and modulate pathophysiological responses.

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NOTICE

Latin American conference on cystic fibrosis

The fifth Latin American Cystic Fibrosis Conference is to take place in Recife, Brazil, on 3-7 April 1993. Further information can be obtained from Dr Fernando de Abreu e Silva, Rua Duque de Caxias 1327/101, Porto Alegre RS, Brazil 90010 (fax (081) 421.2404).