LETTERS TO THE EDITOR

Diagnosis of pulmonary disease in human immunodeficiency virus infection: role of transbronchial biopsy and bronchoalveolar lavage

Dr MH Griffiths and colleagues (July 1989; 44:554–8) recorded a high incidence of complications while performing transbronchial biopsies in patients with HIV infection, whereas the side effects seen with bronchoalveolar lavage were few and unimportant. Their comparison of the risk-benefit ratios of the two procedures encourages use of lavage rather than transbronchial biopsy.

Our experience at the Institute of Infectious Diseases in the University of Verona has been dissimilar in terms both of complications and of sensitivity rate. Bronchoscopy was carried out on 29 HIV infected patients with clinical and radiographic findings that suggested a pulmonary disorder but with an arterial oxygen tension above 50 mm Hg (6·7 kPa). There were none of the important complications described by Griffiths (pneumothorax, haemorrage) with transbronchial biopsy sampling. Lavage was also carried out on each occasion. Techniques were carried out under fluoroscopic guidance and this, plus other factors, may account for the lack of untoward effects in our experience. Fluoroscopic guidance also allowed us to take biopsy specimens from areas showing consolidation on the chest radiograph. This probably improved the diagnostic sensitivity in cases of tuberculous infection (six cases), which may occur more frequently than the data of Dr Griffiths and her colleagues suggest.

The diagnostic sensitivities of the two techniques were similar (76% for transbronchial biopsy and 69% for lavage), though the histological picture available from the biopsy procedure provided more complete microbiological information. This is not surprising as *Pneumocystis carinii* pneumonia (the most frequent opportunist infection in this context) usually results from the reactivation of latent endogenous infection and the organisms may be found in healthy subjects.[1] Thus the demonstration of *P carinii* alone in lavage specimens does not provide proof that it is causing pneumonia in these patients. The high incidence of pneumocystis pneumonia in AIDS justifies an empirical approach to treatment based on clinical and radiograph findings; if a direct diagnostic assessment is required we believe that biopsy provides the best information.

Dr Griffiths and colleagues are correct stating that specimens obtained during bronchoscopy may also be useful for evaluating the response to treatment. For pneumocystis pneumonia, however, this is true only for biopsy as lavage fluid often remains positive weeks after the beginning of treatment, regardless the outcome of the disease.[2] Biopsy samples provide an anatomical picture of the alveolar status and are more reliable than lavage both for diagnosis and for evaluating the evolution of *P carinii* infection in the lung. This to some extent also applies to cytomegalovirus infection as the typical inclusion bodies are often seen without clinical disease. Inclusions indicate active cytomegalovirus infection according to the criteria of the Communicable Diseases Center,[3] but local pathogenicity is disputed.[4] Factors other than fluoroscopic guidance may have played some part in the dissimilar findings in our patients. We believe that transbronchial biopsy still deserves an important place in the investigation of pulmonary disorders in HIV infection.

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1 Weisse K, Welder E. Uber das Vorkommen der segenaunten "Pneumocystis carinii." *Klin Wochenschr* 1954;32:270.
2 Allegra CJ, Chabner BA, Tuazon CV, *et al.* Trimetrexate for the treatment of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1987;317:978–85.
3 Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *Morbidity and Mortality Weekly Record* 1987; 36(suppl):1–5.
4 Naragi S. Cytomegaloviruses. In: Belshe RB, ed. *Human virology*. Littleton, Massachusets: PSG Publishing Company, 1984:887–927.

AUTHOR'S REPLY The difference in the incidence of complications of transbronchial biopsy in our series and Dr Di Perri's series may be partly explained by the smaller numbers in their series (29) than ours (74). Reports on larger series from other centres also record a significant incidence of complications for transbronchial biopsy in HIV infected patients (our refs 12 and 32) and fluoroscopy has not, in the experience of other groups, contributed to a reduced risk. Milligan *et al* (our ref 32) found no significant difference in the incidence of complications or the diagnostic yield between 63 transbronchial biopsies performed with fluoroscopic control and 187 without fluoroscopy in HIV patients being investigated for diffuse pulmonary infiltrates.

It is not clear from the letter of Dr Di Perri and his colleagues what the diagnostic categories of the 29 patients were, but if six had tuberculosis the proportion of patients with pneumocystis pneumonia was probably lower than in our series, and it was in this diagnostic category that complications occurred. Of the 17 serious complications in our series, 16 (14 pneumothorax, two haemorrhage) occurred after transbronchial biopsy in patients with pneumocystis pneumonia.

We do not think that we are missing cases of tuberculosis, as Dr Di Perri suggests, because none of our patients developed tuberculosis during close follow up. It has now been established that there is a genuinely lower incidence of tuberculosis in HIV infected patients in the United Kingdom than in other parts of the world,[1] and this has been attributed to the lower incidence of latent tuberculous infection in the population at risk of HIV infection in this country.

We agree that knowing the histological appearances contributes to a more complete picture of the morbidity of AIDS, but we were unable to attribute any improvement in patient management to this knowledge. The nature of the host response to pneumocystis infection (our largest diagnostic category), as assessed by transbronchial biopsy, did not appear to correlate either with the degree of clinical distress or with the response to treatment. It was the detection of pneumocystis cysts that was important clinically and for this we found bronchoalveolar lavage more effective than transbronchial biopsy, probably because of the larger alveolar volume sampled.

While the presence of *Pneumocystis* may have been recorded in the lungs of subjects other than those with AIDS, those referred to in the work of Weiss *et al* (their ref 1) were not healthy. They were either newborn babies and infants with fatal conditions or old people with generalised illnesses. In practice we have not found any *P carinii* in bronchoalveolar lavage fluid from patients with unrelated conditions or in immunosuppressed patients who did not have clinically important infection. *P carinii* must be regarded as a highly significant finding in a bronchoalveolar lavage specimen. Transbronchial biopsy, even when it gives a negative result, does not alter the clinical significance of this finding.

It has not been our experience that *P carinii* remains detectable by bronchoalveolar lavage for weeks after treatment. On the contrary, the cysts disappear from the lavage fluid within days of the start of treatment; the radiological opacities are slower to clear.

We would agree that finding cytomegalovirus inclusions in bronchoalveolar lavage or transbronchial biopsy specimens is not evidence of important pulmonary disease but it does indicate the presence of systemic cytomegalovirus infection; morbidity in less accessible sites, such as the eye or the central nervous system, might then be attributed to this infection.

We remain unconvinced of any benefit to these patients gained by taking transbronchial biopsy specimens.

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1 Watson JM, Gill ON. HIV infection and tuberculosis. *Br Med J* 1990;300:63–5.

Diaphragmatic paresis: pathophysiology, clinical features, and investigation

We were interested to read the review by Dr John Gibson (November 1989;44:960–70). Dr Gibson supports the attractive and widely held hypothesis that the "shrinking lung" syndrome of systemic lupus erythematosus is due to diaphragm weakness. In a recent study using a wide range of tests for respiratory muscle strength, however, we concluded that the loss of lung volume observed in 12 patients with the syndrome was not explained by an abnormality of the diaphragm or phrenic nerves in the absence of a generalised myopathy or myositis.[1] We believe that the papers quoted provide less than convincing evidence of isolated bilateral diaphragm weakness, as they all used a limited set of tests to assess diaphragm function and most studied small numbers of patients. In the largest study[2] maximum transdiaphragmatic pressure was measured during static occluded efforts alone, and compared with a normal range obtained from 10 normal males. Not

surprisingly, reduced values were found in 11 out of 30 women, though these would have been considered normal if compared with normal ranges for female patients. We therefore find it hard to agree that diaphragmatic myopathy is the cause of the shrinking lung syndrome of systemic lupus erythematosus.

Dr Gibson quotes two papers which appear to suggest that patients with isolated bilateral diaphragm weakness or paralysis can develop hypercapnia or hypoventilation, but we do not believe that these contradict our paper, in which we found no evidence of chronic hypercapnia or nocturnal hypoventilation in six patients with longstanding bilateral diaphragm paralysis who had otherwise normal lungs, respiratory muscles, and chest wall.[3] Most of the patients reported in Newsom Davis's original paper[4] had diffuse weakness of the respiratory muscles as well as the diaphragm. The two papers quoted by Dr Gibson are case reports: in the first the patient was nursed supine but recovered fully when allowed to adopt a more upright posture.[5] In the second the patient had undergone a recent thoracotomy, which is likely to have impaired rib cage and chest wall movements.[6] By contrast we described patients with proved bilateral diaphragm weakness who have remained otherwise well for up to 10 years.

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1 Laroche CM, Mulvey DA, Hawkins P, Walport M, Strickland B, Moxham J, Green M. Diaphragm strength in the "shrinking lung" syndrome of systemic lupus erythematosus. *Q J Med* 1989;**265**:429–39.
2 Wilcox PG, Stein HB, Clarke SD, Pare PD, Pardy RC. Phrenic nerve function in patients with diaphragmatic weakness and systemic lupus erythematosus. *Chest* 1988;**93**:352–8.
3 Laroche CM, Carroll N, Moxham J, Green M. Clinical significance of severe isolated diaphragm weakness. *Am Rev Respir Dis* 1988; **138**:862–6.
4 Newsom Davis J, Goldman M, Lok L, Casson M. Diaphragm function and alveolar hypoventilation. *Q J Med* 1976;**45**:87–100.
5 Sandham JD, Shaw DT, Guenter CA. Acute supine respiratory failure due to bilateral diaphragmatic paralysis. *Chest* 1977;**72**:96–8.
6 Kreitzer SM, Feldman NT, Saunders NA, Ingram RH. Bilateral diaphragmatic paralysis with hypercapnic respiratory failure. *Am J Med* 1978;**65**:89–95.

AUTHOR'S REPLY Drs Laroche and Green take me to task over two points where their own data or interpretations differ from those of other authors.

The likely contribution of diaphragmatic weakness to the "shrinking lung" syndrome of systemic lupus erythematosus is supported by four clinical studies (refs 70–74 in my article) and by the only published clinicopathological study of the diaphragm in this condition (ref 72). The reasons for the different results obtained by Laroche and others[1] are not clear but one factor may be patient selection. They specifically excluded patients with "generalised muscle weakness due to coexistent polymyositis" (criteria not stated), whereas other authors made no such exclusions, using only a descriptive clinicophysiological and radiographic definition of the "shrinking lung" syndrome. It is likely that other factors are important in restricting lung expansion in some patients but the evidence overall still favours diaphragmatic weakness as the major factor in most cases of the "shrinking lung" syndrome as usually defined.

The second controversial area concerns the role of bilateral diaphragmatic paralysis in the development of hypercapnia and nocturnal hypoventilation. I would agree that bilateral diaphragmatic paralysis is not necessarily associated with *daytime* hypercapnia. I also agree that the patients reported by Newsom Davis *et al* (ref 10) had generalised respiratory muscle weakness and, as I emphasised in my article, this is the usual setting in which bilateral diaphragmatic paralysis is seen. The evidence against *nocturnal* hypoventilation as a consequence of bilateral diaphragmatic paralysis per se is, however, less convincing. Studies in normal subjects suggest that such patients would be most vulnerable during rapid eye movement (REM) sleep, when the other respiratory muscles are likely to be inhibited. Such an effect was indeed well documented in one patient with apparently "pure" bilateral diaphragmatic paralysis who had gross hypoventilation and periods of "central" apnoea during REM sleep.[2] Unfortunately, detailed sleep studies were not reported by Laroche *et al* (ref 11), but it is noteworthy that the two of their six patients with the longest periods of REM sleep showed decreases in arterial oxygen saturation as large as 20% and 27%. Clearly, more studies are desirable but the rarity of such "pure" cases makes this difficult to achieve. Meanwhile my conclusion that, in the presence of normal function of other respiratory muscles, bilateral diaphragmatic paralysis has less profound consequences than previously described remains a fair summary of the published data.

G J GIBSON

1 Laroche CM, Mulvey DA, Hawkins P, *et al*. Diaphragm strength in the "shrinking lung" syndrome of systemic lupus erythematosus. *Q J Med* 1989;**265**:429–39.
2 Stradling JR, Warley ARH. Bilateral diaphragm paralysis and sleep apnoea without diurnal respiratory failure. *Thorax* 1988;**43**:75–7.

NOTICES

International symposium on respiratory psychophysiology

The 10th International Symposium on Respiratory Psychophysiology will be held at the University of Amsterdam on 21 and 22 September 1990. The conference will include workshops, limited to 25 participants each. Submission of abstracts relevant to the symposium themes for oral or poster presentations is invited. For further information please contact Dr B Garssen, Department of Medical Psychology, Academic Medical Centre, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands.

British Sleep Society

The second annual scientific meeting of the British Sleep Society will be held in Leeds on 24–26 September 1990. The programme will include sessions on narcolepsy, parasomnias, developmental aspects of sleep disorders, measures of wakefulness, methodology, sleep in the postoperative period, and the pharmacology of sleep disturbances. Free papers will be presented both by poster and verbally and abstracts are invited. For further information please contact Dr I Hindmarch, University Department of Psychology, Leeds LS2 9JT (fax 0532 421639) or Dr CD Hanning, Sleep Disorders Clinic, Leicester General Hospital, Leicester LE5 4PW (0533 584602 (direct line); fax 0533 737991).