LETTERS TO THE EDITOR

Bronchoalveolar lavage as a research tool

I enjoyed the timely review of bronchoalveolar lavage by Drs E H Walters and P V Gardiner (September 1991;**46**:613–8) but take exception to several of their conclusions. They referred to their earlier work[1] in which ^3H_2O was incorporated into the blood or airspace fluid and its movement between these compartments was measured. From this they calculated that 39% of the aspirated fluid flowed into the airspaces from the blood. I would argue that exchange of ^3H_2O between these compartments is driven by concentration differences and would occur regardless of whether or not there was any net movement of fluid.

Net movement of fluid from the blood into the airspaces would dilute solutes present in the airspaces and the authors cite decreases in methylene blue concentrations seen by themselves and others to support their hypothesis. They did not, however, rule out diffusion of this small solute out of the airspaces or its reduction to colourless derivatives. Decreases in airway concentrations of ^{99m}Tc colloid, which they also observed, may be related to sedimentation or adherence of this indicator to epithelial membranes. When soluble macromolecules (labelled albumin or labelled dextran) have been instilled into the airspaces by several different investigators, no decreases in concentrations were detectable (see, for example, ref 2).

Bulk movement of water across the pulmonary epithelium is constrained by the high reflection coefficients of the epithelium to both small and large solute molecules,[3] and movement of electrolytes and ^{14}C urea across the epithelium is too slow to suggest significant movement of fluid between these compartments during lavage.[4] It can be calculated from these reflection coefficients that ultrafiltration of solute free fluid into the airspaces would require extreme pressures, which are not generated during lavage (> 5000 mm Hg).

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1 Kelly CA, Fenwick JD, Corris CA, Fleetwood A, Hendrick DJ, Walters EH. Fluid dynamics during bronchoalveolar lavage. *J Appl Pathol* 1983;55:1262–8.
2 Effros RM, Mason GR, Hukkanen J, Silverman P. New evidence for active fluid transport in edematous rat lungs. *J Appl Pathol* 1989;**66**: 906–19.
3 Effros RM, Mason GR, Sietsema K, Hukkanen J, Silverman P. Pulmonary epithelial sieving of small solutes in rat lungs. *J Appl Pathol* 1988;**65**:640–8.
4 Effros RM, Feng D, Mason G, Sietsema K, Silverman P, Hukkanen J. Solute concentrations of the epithelial lining fluid in anesthetized rats. *J Appl Pathol* 1990;**68**:275–81.

AUTHOR'S REPLY I am grateful for the comments on our editorial on bronchoalveolar lavage from Professor Effros.

Professor Effros perhaps assumes that the clinical technique of bronchoalveolar lavage is essentially the same as his elegant in vitro model of the fluid filled, perfused animal lung preparation. I don't believe that this is really the case, and calculations and assumptions based on the latter are unlikely to apply to the former. Our data would suggest that bronchoalveolar lavage distorts the epithelial barrier in the bronchopulmonary segment studied, either by the excessive local inflation at the time of injection of fluid or at the time of aspiration, or both, resulting in the opening up of "unphysiological" intercellular pores with much lower reflection coefficients than are found by applying osmotic stimuli on relatively undisturbed whole lungs.

In our studies of water and solute "fluxes" at bronchoalveolar lavage to which he refers (his ref 1) the large influxes of water into the lavage fluid at aspiration were remarkably similar whether calculated indirectly by dilution of methylene blue or large molecular colloid "markers" or directly measured from bidirectional movements of tritiated water. It is difficult to see how the sorts of potential artefacts which Professor Effros quite reasonably mentions could give such consistency. Our studies with tritiated water were precipitated only by the finding that larger molecular weight markers were diluted to a degree that could not reasonably be explained merely by incorporation of the putative lung epithelial lining fluid.

In addition, more recent work in our laboratory indicates that relatively large influxes of urea as well as water occur into bronchoalveolar lavage fluid at aspiration, even after minimal dwell time. This again emphasises that the assumptions that Professor Effros has built up from his studies on relatively stable pulmonary epithelial membranes, and even in his more recent whole lung lavage model in rats (his ref 4), don't seem to apply to the acute and potentially locally disruptive procedure of bronchoalveolar lavage, which seems to induce some process of filtration across the bronchopulmonary epithelium, as well as movements due to diffusion alone.

Finally, however, I need to point out that our emphasis has not really been on trying to define the mechanisms by which water and solutes move between blood stream and lavage fluid during the procedure, which are likely to be complex and multifactorial. Without better data on the surface area-volume-pressure relationships these are likely to remain somewhat speculative. We have been more interested in merely pointing out that relatively large movements of water and solutes between blood and lavage fluid do seem to be occurring at bronchoalveolar lavage and that conventional presumptions about the dilution and calculation of epithelial lining fluid are likely to be highly oversimplistic.

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BOOP and COP

I read with interest the editorial on obliterative bronchiolitis organising pneumonia and cryptogenic organising pneumonitis (BOOP and COP) by Dr D M Geddes (August 1991; **46**:545–7) and agree with his conclusion that BOOP and COP are essentially the same condition. I would like to point out one error in his references. Reference 2 in Dr Geddes's editorial was not "anonymous" but by the German pathologist W Lange, who described the pathological lesion of BOOP or COP as early as 1901 in his paper entitled 'Über eine eigenthümliche Erkrankung der kleinen Bronchien und Bronchiolen (Bronchitis et Bronchiolitis obliterans)" (*Dtsch Arch Klin Med* 1901;**70**:342–64). He reported on two patients who presented with a pneumonic illness with fever, cough, increasing dyspnoea, and crackles on auscultation. The postmortem findings were described by Lange in detail, and he found organising exudates with plugs of granulation and young connective tissue that were located within small bronchi, bronchioli, and alveoli. These were exactly the features of the lesion now called BOOP or COP. Lange already recognised that the plugs always extend from the walls of bronchioles into the alveolar lumen, and never grow from the alveolar wall itself.

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REPLY We disagree that Lange was describing COP because in his two cases the disease evidently was affecting all orders of bronchioli and reached as far proximally as to take in small bronchi. It is fairly clear from this that Lange's patients would have had an obstructive pattern of disease whereas COP/BOOP is characterised by a restrictive defect, being largely limited to alveoli, alveolar ducts, and only the smaller bronchioli. We are quite sure, however, that German pathologists before Lange described all the pathological features of COP in patients dying with resolving bacterial pneumonia. The feature that distinguishes COP/idiopathic BOOP is the cryptogenic/idiopathic nature of the condition.

It appears that an error occurred in the final draft of the article as the name Lange was omitted from reference 2 and the word "anonymous" inserted in error.

With regard to the site at which the granulation tissue plugs attach to the interstitium in COP/BOOP, the alveoli affected extend out to the periphery of the acinus, well away from the supplying bronchiole. It therefore seems unlikely that they would not have an alveolar attachment. Review of our cases confirms that they do indeed attach to alveolar walls.

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Vertebral fractures in steroid dependent asthma and involutional osteoporosis: a comparative study

We read with some interest the study by Dr M Luengo and colleagues (November 1991; **46**:803–6).

In this study the authors suggest that, in the presence of corticosteroid associated osteoporosis, bone densitometry is less useful for detecting patients at risk of developing vertebral fracture than in involutional (postmenopausal) osteoporosis. This is contrary to our own experience with dual energy *x* ray

absorptiometry (DEXA) in corticosteroid associated osteoporosis. We reported to the summer 1991 meeting of the British Thoracic Society[1] our experience of 19 patients (13 female) with corticosteroid dependent asthma. Twelve of these patients had sustained at least one vertebral compression fracture. The mean corticosteroid dose and treatment duration for this fracture group was 10·1 mg prednisolone/day for 13·1 years and 13·9 mg prednisolone/day for 9·6 years in those patients without fracture (NS). The mean L2-L4 density was significantly lower in those patients with fractures (0·797 g/cm^2 versus 1·143 g/cm^2, $p < 0·0001$). The mean neck of femur density was also significantly lower in those patients with fractures (0·718 g/cm^2 versus 0·901 g/cm^2, $p < 0·005$). The study by Dr Luengo and colleagues used dual photon densitometry, which is known to be a less precise measure than DEXA,[2] and this may explain why in their study, though spinal density was higher in asthmatic patients without fractures, the difference was not statistically significant. It would appear therefore that a single measure of L2-L4 density by DEXA is a useful screening test for corticosteroid associated osteoporosis.

Finally, in their discussion the authors ignore the effect of the menopause on the changes described. There is significant evidence that premenopausal women, who (though it is not stated) probably make up most of "group 1," are protected from corticosteroid associated osteoporosis, presumably by the effects of oestrogen.[3]

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1 Anderson K, Gallacher SJ, Fenner JAK, Jenkins A, Banham SW, Boyle IT. The effect of intermittent pamidronate infusions on bone metabolism in corticosteroid dependent asthma [abstract]. *Thorax* 1991;**46**:769P.
2 Holbrook TL, Barrett-Connor E, Klauber M, Sartoris D. A population-based comparison of quantitative dual-energy *x*-ray absorptiometry with dual-photon absorptiometry of the spine and hip. *Calc Tiss Int* 1991;**49**:305–7.
3 Boyce BF, Gallacher SJ, Byars J, Adamson B, Boyle IT. No osteoporosis found in premenopausal patients on long-term corticosteroid therapy for asthma [abstract]. *J Bone Min Res* 1991;**6**(suppl 1):104.

AUTHORS' REPLY We thank Dr Gallacher and colleagues for his interest in our article comparing bone mineral mass as a predictor for vertebral fractures in steroid dependent asthma. In our study we found that the mean L2-4 density was lower in steroid dependent patients with vertebral fractures than in those without fractures. The difference, however, did not reach statistical significance. In contrast, they found that the values obtained by bone densitometry were significantly lower in steroid dependent asthmatic patients with fractures than in patients without fractures.

Unfortunately, neither their letter nor the abstract of their work offers information about important aspects such as the age of subjects and the selection of patients for their study. We studied 99 consecutive steroid dependent asthmatic patients and detected vertebral fractures in 32 (prevalence 32%) while they investigated 19 patients, 63% of whom suffered fractures. This very high prevalence of vertebral fractures suggests that selection bias operated in the inclusion of patients in their study. We also suspect that in this study patients with fractures were much older than subjects without fractures and thus comparison of absolute values of bone density between the two groups could be misleading.

We agree that the menopause should be considered as an independent factor in patients having continuous steroid treatment. But the suggestion that the bone of premenopausal women is "protected" against the deleterious effect of steroids cannot be substantiated by the study of Boyce *et al* (their reference 3) because this did not include a control group of asthmatic patients not having steroid treatment. On the other hand, it has been found that steroid treatment decreases osteocalcin concentrations in both premenopausal and menopausal women. As osteocalcin is a marker of bone formation this finding also argues against the hypothesis of Dr Gallacher and his colleagues.

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Bronchial compression as a result of lung herniation after pneumonectomy

We read with interest the paper of Dr K F Whyte and others (November 1991;**46**:855–7) concerning a 40 year old housewife with a right pneumonectomy syndrome. A thoracotomy to attempt a corrective procedure was unsuccessful because of right apical pleural adhesions and the patient remained severely disabled.

We have seen five patients with the right pneumonectomy syndrome in the past two years, seven months to 13 years after right pneumonectomy. All have been treated with the implantation of an expandable mammary prosthesis into the right hemithorax to correct the position of the mediastinum and the left lung. Two patients are the subject of a report that will be published.[1]

All five patients experienced an immediate and important reduction of dyspnoea. Pulmonary function improved and bronchoscopy showed a considerable decrease of bronchial compression in all patients. The improvement was sustained in four patients; in the other patient, who had the pneumonectomy 13 years previously, a cicatricial hernia occurred at the site of the implantation. A Marlex Mesh patch has been attached to the thoracic wall, and a new expandable prosthesis will be implanted.

We believe that implantation of an expandable mammary prosthesis is the treatment of choice in the right pneumonectomy syndrome.

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1 Janssen JP, Brutel de la Rivière A, Carpentier Alting MP, Westermann CJJ, Bergstein PGM, Duurkens VAM. Post-pneumonectomy syndrome in adulthood: surgical correction using an expandable prosthesis. *Chest* (in press).

School microepidemic of tuberculosis

We read with interest the recent paper by Dr Bredin and colleagues (December 1991;**46**: 922–3). A recent outbreak of tuberculosis in Leeds also infected principally school age children.[1]

In 1988 a 23 year old woman from a poor, predominantly white community within the city, designated by the council as an area of deprivation, presented with smear positive pulmonary tuberculosis. Screening of contacts revealed 10 with pulmonary tuberculosis, eight of whom were children (age range 4–8 years). All but two of the children and one adult were asymptomatic; in six cases the place of contact was the school or community centre. A further 10 children had unexplained grade 2 or 3 positive Heaf test responses and received chemoprophylaxis with isoniazid and rifampicin. None of those infected had received neonatal BCG immunisation. This outbreak demonstrates that, despite the declining incidence of tuberculosis, poor indigenous communities in England remain at risk of tuberculosis. Poor nutrition and housing probably contributed to this outbreak; socioeconomic details were not provided by Dr Bredin and colleagues but such factors may have played a part in the size of their microepidemic. None of our subjects treated with chemoprophylaxis have developed tuberculosis so far; this contrasts with the Cork epidemic, where the brother of the probable index patient developed tuberculosis following chemoprophylaxis, possibly because of his heavy exposure.

Dr Bredin and colleagues also noted that, of 324 children who had received neonatal BCG, 63% had a grade 1 or 2 Heaf response, compared with 85% of 262 children who had not received neonatal BCG; but they were unable to determine the protective effect of neonatal BCG because the number of active tuberculosis cases was too small for statistical comparison. We have recently examined the effects of our neonatal BCG immunisation programme, which is offered to all Asian babies, on the Heaf status of schoolchildren routinely tested at the age of 12–13 years.[2] Of 5013 non-Asian children tested, 8% had a Heaf test response of grade 2 or more, compared with 47% of 366 Asian children tested. On the basis of current Department of Health guidelines, 8% of non-Asian and 75% of Asian children had appropriate immunity, avoiding the need for repeat BCG immunisation. The high prevalence of grade 1 and 2 Heaf responses in Cork, and the surprising observation that rates were higher in children who had not received infant BCG immunisation, presumably reflects a higher prevalence of tuberculosis in the Irish community. We believe that, as suggested in a recent editorial in the *British Medical Journal*,[3] neonatal BCG immunisation should be offered routinely in areas of social deprivation in the United Kingdom.

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1 Teale C, Cundall DB, Pearson SB. Outbreak of tuberculosis in a poor urban community. *J Infect* 1991;**23**:327–9.
2 Teale C, Cundall DB, Pearson SB. Heaf status 12 years after infant BCG immunisation [abstract]. *Thorax* 1989;**44**:843P.
3 Conway S. BCG vaccination in children. *BMJ* 1990;**301**:1059–60.