Long acting sulphonamide type drugs may be associated with alveolitis more commonly than is currently realised. Minor degrees of dyspnoea may not be picked up by doctors unaware of the association. Routine three monthly spirometry and possibly chest radiography may be indicated for people taking these drugs. Two particular aspects of our patient's history are the previous dapsone reaction, suggesting generalised hypersensitivity to sulphur drugs, and the onset of lung disease despite her taking corticosteroids.

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Cardiovascular and hypokalaemic effects of inhaled salbutamol, fenoterol, and isoprenaline

SIR,—In their paper (February 1989;**44**:136–40) Dr J Crane and coworkers concluded that fenoterol evoked more pronounced hypokalemia and stronger ($beta_1$ mediated) inotropic responses than did salbutamol. We would, however, like to raise some questions regarding interpretations and conclusions which have not been addressed by Dr Crane and his colleagues.

Results concerning the main parameter of the study (plasma potassium concentration) are presented in terms of changes from baseline but with no baseline values given. Placebo caused a substantial increase in plasma potassium, indicating that baseline values were not stable. Were baseline values identical on the different days? The increase in potassium after placebo was actually greater than the reduction after salbutamol—would this increase have been identical on the different days? As beta adrenoceptors can be up or down regulated (time and dose dependent changes) and receptors in different tissues may respond differently (see, for example, Harvey *et al*[1]) it would also have been of interest to know if there were possibilities for carry over effects between treatments—what time span was required between studies and are there data on effects on sodium-potassium ATPase activity on renewed beta stimulation after provocation with a beta agonist? Tolerance may well have developed after a dose of a long acting agonist such as fenoterol.

The authors state that the greater cardiac stimulation apparently afforded by fenoterol was due to more pronounced $beta_1$ adrenoceptor activation. The human heart, however, is richly endowed with $beta_2$ adrenoceptors, which in most studies comprise about one third of the cardiac beta adrenoceptor population[2]; functionally these $beta_2$ adrenoceptors seem to be even better coupled to adenylate cyclase than are the $beta_1$ adrenoceptors (see, for example, Kauman and Lemoine[3]). Thus fenoterol may well have stimulated the heart via $beta_2$ adrenoceptor stimulation. Furthermore, earlier studies did not show any difference in $beta_2$ selectivity between salbutamol and fenoterol given in therapeutic doses.[4]

The time dependence of the effects, seen in relation to the pharmacokinetics of the drugs, has not been adequately discussed. Lipid solubility (which is greater for fenoterol) and local metabolism (which is extensive for the rapidly *O* methylated catecholamine isoprenaline) are factors to be considered. Cumulation of the three drugs may have been quite different with the protocol used. No plasma concentration-effect evaluation was performed. Furthermore, the authors provide no evidence that fenoterol and salbutamol are equipotent on a milligram for milligram basis with regard to bronchodilatation (the recommended dosages for fenoterol are lower than those for salbutamol in Sweden)—were equipotent doses studied?

Most importantly, however, we think that it is unjustified to extrapolate findings with single doses of the drugs given to healthy volunteers to chronic treatment in asthmatic subjects. The study does not allow any conclusions about chronic effects of fenoterol or salbutamol (in adequate therapeutic dosages) in the long term—that is, when receptor adaptation, etc, has taken place and most likely modified the various, in our opinion mainly $beta_2$ mediated, responses studied.

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AUTHORS' REPLY Drs Larsson and Hjemdahl raise questions regarding interpretations and conclusions not addressed in our paper comparing the extrapulmonary effects of fenoterol, salbutamol, and isoprenaline.

With regard to hypokalaemia, mean (SEM) baseline values were similar on the four study days: placebo 4·0 (0·12) mmol/l, salbutamol 4·2 (0·12) mmol/l, fenoterol 4·0 (0·08) mmol/l, isoprenaline 4·1 (0·12) mmol/l. Studies were undertaken a week apart and treatments administered randomly according to a balanced Latin square design. This design minimises any systematic carry over effect and the time interval makes altered beta receptor regulation unlikely, particularly as it followed a single administration. The rise in plasma potassium following placebo and, more importantly, the resting state is of interest. We have repeatedly observed it

ourselves,[1] as have others.[2 3] We are uncertain of the reasons but the withdrawal of sympathetic activity and concomitant redistribution of potassium would seem the most likely possibility. We have also consistently observed a lengthening of the QS2 interval with rest, consistent with sympathetic withdrawal.

As discussed in our paper a positive chronotropic response may be associated with $beta_2$ and $beta_1$ stimulation, but a positive inotropic response with an increase in systolic blood pressure is due to $beta_1$ stimulation.[4] We observed a significantly greater positive inotropic response and increase in systolic blood pressure with fenoterol than with salbutamol.

We agree with the authors that at recommended doses there is no difference between the beta selectivity of fenoterol and salbutamol. As we discussed in our paper, however, patients may not adhere to the recommended doses during severe attacks of asthma and we feel justified in examining the effects of higher doses of these agents.

The pharmacokinetics have not been discussed because they are not relevant to this study. We wished to examine the extrapulmonary effects of these agents in normal volunteers, in doses that might be used in the clinical setting by patients suffering acute attacks of asthma. Our interest was with the pharmacodynamics, not kinetics. We agree with the authors that isoprenaline will be rapidly metabolised locally and that fenoterol will accumulate—indeed, we specifically pointed this out in our paper.

We have not attempted to extrapolate directly to chronic asthma but have simply observed significant differences in normal volunteers that may have relevance to asthmatic patients.

The authors do, however, raise an extremely important point regarding the lower recommended doses of fenoterol compared with salbutamol in Sweden. The recommended doses are similar in New Zealand for salbutamol and fenoterol. Fenoterol is dispensed by metered dose inhaler as 200 μg/puff compared with salbutamol 100 μg/puff; the common use of two puffs at each treatment means that in practice patients regularly use a dose of fenoterol that is twice that of salbutamol. Furthermore, there are other international differences in the concentrations of fenoterol nebuliser solutions. The standard solution in New Zealand contains 5 mg/ml of fenoterol while in Canada the solution contains 1 mg/ml. The reasons for these international differences require closer examination and explanation.

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Adrenal function in patients with active tuberculosis

SIR,—I read with interest the study of metabolic changes in tuberculosis, reported by Dr DJ Barnes and colleagues (May 1989;44:422–4), but their findings in respect to serum sodium changes in a Melanesian population differ from observations on English patients.

These workers found that 41% of their patients with tuberculosis were hyponatraemic. In a series of 125 patients with tuberculosis I found that only 24% had abnormally low serum sodium concentrations, with a lowest value of 126 mmol/l. The entire series tended to have a low sodium level with a mean value of 135·9 (SD 4·34) mmol/l.

Dr Barnes and colleagues failed to identify adrenal dysfunction as a common problem in patients with active tuberculosis in the tropics, and postulated that salt depletion or vasopressin excess might be alternative explanations for hyponatraemia. The discrepancy between these two populations points to salt depletion in the tropics as the additional factor.

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AUTHORS' REPLY We would like to thank Dr Mustchin for his interest in our paper. His English patients certainly had a lower incidence of hyponatraemia than our Melanesian population (24% versus 41%; $p < 0·02$, χ^2 test). We would agree that the most likely cause for our higher prevalence of hyponatraemia is salt depletion. Mild hyponatraemia is a common finding on presentation in febrile illness in the tropics. It is our impression that it is just as common in pneumonia, malaria, etc, as it is in tuberculosis; but this has not been formally studied. Ideally, we would have liked to have measured the serum and urine osmolalities in our patients, but this was not logistically possible.

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