subjects there was an increase in bronchial hyperresponsiveness only during the last two weeks of the study, but by the end of four weeks this increase had disappeared. In the study of Vathenen et al (ref 7) with eight asthmatic subjects it was observed that a (rebound) increase in hyperresponsiveness occurred, not whilst using the β agonist but afterwards. In our own study (ref 14) an increase in hyperresponsiveness was observed when using a β agonist in a selected group of 15 patients. These 15 patients were selected on the condition that they had not used any β agonists or blockers for one year before the start of the study. They were part of a much larger group of 144 patients who, on average, did not show an increase in bronchial hyperresponsiveness during the use of the β agonist (ref 1, not presented in the table). Looking at the presented table, it seems that the more patients involved in these studies the less clear is the adverse prognosis of bronchial hyperresponsiveness during the continuous use of a bronchodilator. This underlines our conclusion that only in subgroups of patients might the continuous use of a β, adrenergic drug have an adverse effect on bronchial hyperresponsiveness. The only exception seems to be the study of Sears and Taylor themselves (ref 3) with a relatively large number of 64 patients. However, this is the only study in which patients were allowed to use anti-inflammatory drugs as well as their bronchodilator drugs.

As Sears and Taylor have already acknowledged, the observed changes in hyperresponsiveness were small. They were all between 0.5 and 1.5 doubling doses of the challenge test, which is virtually similar to the repeatability of the challenge test and is therefore of doubtful clinical significance.

The purpose of writing our editorial was not to present a neutral position in this important issue but to show that the general fear that exists among doctors and patients about the chronic use of bronchodilators does not need to be justified by the data available at this moment. We did not, and not, doubt that bronchodilators probably have a (small) negative influence on the long term prognosis of bronchial hyperresponsiveness in certain groups of asthmatic patients. Subgroup analyses of our own data have shown that especially allergic hyperresistant asthmatic patients seem to have an increased progression of asthma with continuous use of a β agonist.1 Another important issue which still has to be settled is what additional bronchodilator drug should be used (and in what dose) when the patient receives a combination of an anti-inflammatory drug and a bronchodilator.

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Extrapulmonary effects of fenoterol and salbutamol in normal subjects

Newnham et al have attempted the difficult task of trying to dissect relative β₁ and β₂ mediated cardiovascular responses to large doses of salbutamol and fenoterol in normal subjects with a low dose of atenolol (June 1993;48:656-8). There are two issues: firstly, the comparative responses to similar doses of these agents by inhalation and, secondly, their selectivity at the β₂ receptor.

Newnham et al showed that salbutamol and fenoterol in doses of 1 mg and 3 mg from metered dose inhalers led to similar increases in heart rate, stroke distance, and tremor, with fenoterol causing a slightly greater fall in serum potassium concentration and a greater rise in systolic blood pressure than salbutamol. Their findings suggest smaller differences between higher doses of salbutamol and fenoterol in cardiovascular effects than other studies, whether the comparisons have been made in vitro, in vivo, or in different species.12 Invariably fenoterol has been found to be more potent in large doses than salbutamol. When intravenous preparations have been found a 2-4 times greater effect on heart rate with fenoterol, and this has led to a tenfold difference in the concentration of intravenous solutions used rout- inely (500 μg/ml salbutamol compared with 5 μg/ml fenoterol). For the different findings of Newnham et al unexplained.

The attempts by the authors to dissect relative β₁ and β₂ effects have failed as they have shown that atenolol significantly at- tenuates the β₁ mediated effect on heart rate, tremor, and serum potassium concentration. Other designs based on studies by Wellstein et al10 or Hall et al13 may enable such relative β₂ receptor specificity to be shown.

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AUTHORS' REPLY
In reply to the letter of Crane et al there are some fundamental issues which, to our knowledge, are not discussed in the paper, require further clarification.

The purpose of our study was not to assess the relative potency of fenoterol and salbutamol, which requires careful study in asthmatic subjects to ascertain relative bronchodilator and systemic β₂ receptor activity. The 25 mg dose of atenolol in our study was chosen on the basis of it producing relatively selective β₂ blockade. It is, however, well documented that atenolol displays dose related β₁ blockade,13 and so it is not, per- haps, surprising that even a 25 mg dose produced a degree of β₁ antagonism. The impor- tant point is that a comparable degree of attenuation occurred with heart rate and potassium responses, both of which have been shown to be β₂ mediated.14 Indeed, this occurred to the same extent with both feno- terol and salbutamol.

If fenoterol had stimulated cardiac β₁ receptors to a greater degree than salbuta- mol, one would have predicted atenolol to have antagonised the chronotropic response to fenoterol more than salbutamol. This was clearly not the case, with the percentage attenuation by atenolol at the 4 mg dose being 14% for fenoterol and 16% for salbu-tamol. The percentage attenuation of the systolic blood pressure was also comparable for both salbutamol and fenoterol (8%). Thus, whilst fenoterol may exhibit greater β₂ potency, there is no evidence for it being less selective in terms of relative car- diac β₁/β₂ receptor stimulation. It is also worth pointing out that in a study from Windom et al10 in asthmatic subjects there was no difference in either chronotropic or systolic blood pressure responses to fenoterol and salbutamol, in contrast with isoprenaline which produced greater effects, presumably β₁ adrenoceptor mediated.

Our in vivo data are indeed supported by evidence in human right atria,15 showing that the relative pA₂ values for propranolol (β₂ antagonist) and ICI 18 551 (β₁ antagonist) were 5.47 and 8.24 respectively, for antagon- ism of the inotropic response to fenoterol. Taken together we believe that the body of evidence supports the hypothesis that the effects of fenoterol on the human heart are predominantly stimulated by cardiac β₂ receptors.