subjects there was an increase in bronchial hyperresponsiveness only during the first 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 \( \beta \) agonist but afterwards. In our own study (ref 14) an increase in hyperresponsiveness was observed when using a \( \beta \) agonist in a selected group of 15 patients. These 15 patients were selected on the condition that they had not used any \( \beta \) agonists or \( \beta \) 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 \( \beta \) 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 \( \beta \) 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-inflammato-ry drugs as well as their bronchodilator drugs.

As Sears and Taylor have already acknowledged, the observed changes in hyper-responsiveness are small. They found an all-or-none 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 seem 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 hyper-responsible asthmatic patients seem to have an increased progression of asthma with continuous use of a \( \beta \) agonist.1 Another important issue which still has to be settled is what additional bronchodilator drug should be used, or in what dose, when the patient receives a combination of an anti-inflammato-ry drug and a bronchodilator.

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Letters to the editor

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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 \( \beta_1 \) and \( \beta_2 \) 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 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 salbuta-mol and fenoterol than previous findings, but other studies, whether the comparisons have been made in vitro, in vivo, or in different species.1 Invariably fenoterol has been found to be more potent in large doses than salbutamol. Moreover, intravenous preparations have 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 mg/ml salbutamol compared with 50 mg/ml fenoterol). To restate our own findings of Newnham et al are unclear.

The attempts by the authors to dissect relative \( \beta_1 \) and \( \beta_2 \) effects have failed as they have shown that atenolol significantly at-tenuates the \( \beta_2 \) mediated effect on heart rate, tremor, and serum potassium concentration. Other designs based on studies by Wellstein et al or Hall et al may enable such relative \( \beta_2 \) 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, if discussed in the paper, require further clarification.

The purpose of our study was not to assess the relative potency of fenoterol and salbuta-mol, which requires careful isometric and as-thmatic subjects to ascertain relative bron-chodilator and systemic \( \beta_2 \) receptor activity. The 25 mg dose of atenolol in our study was chosen on the basis of producing relatively selective \( \beta_2 \) blockade. It is, however, well documented that atenolol displays dose related \( \beta_2 \) blockade, and so it is not, per-haps, surprising that even a 25 mg dose produced a degree of \( \beta_2 \) antagonism. The im-portant point is that a comparable degree of attenuation occurred with heart rate and potassium responses, both of which have been shown to be \( \beta_2 \) mediated.1 Indeed, this occurred to the same extent with both feno-terol and salbutamol.

If fenoterol had stimulated cardioselective \( \beta_2 \) 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 fenoterol and salbutamol (8%). Thus, whilst fenoterol may exhibit greater \( \beta_2 \) potency, there is no evidence for it being less selective in terms of relative car-diac \( \beta_1/\beta_2 \) receptor stimulation. It is also worth pointing out that in a study from Windom et al 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 \( \beta_1 \) adrenoceptor mediated.

Our in vivo data are indeed supported by in vitro data in human right atria, showing that the relative \( \alpha_1 \) values for practolol (\( \beta_2 \) antagonist) and ICI 18 551 (\( \beta_1 \) antagonist) were 5.47 and 8.24 respectively, for antagonism of the isotropic 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 caused by stimulation of cardiac \( \beta_2 \) receptors.

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AUTHORS’ REPLY

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Thorax 1994 49: 191
doi: 10.1136/thx.49.2.191-a

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