double-blind fashion 15 min before allergen challenge. Airway calibre was monitored by FEV_1 for 4 h after the end of the challenge. Salbutamol and salmeterol completely abolished the early phase of bronchoconstriction in the first 120 min after challenge: the area under the FEV_1-time curve was inhibited by a mean of 90% for salbutamol and 119% (net bronchodilatation) for salmeterol ($p < 0.005$ *vs* placebo). However, in the second 120 min salbutamol did not differ significantly from placebo while salmeterol provided sustained bronchodilation throughout the 240 min. Neither salbutamol nor salmeterol significantly altered LTE_4 excretion in the first 2 h after challenge but caused modest reductions in the second 2 h collection (figure). There was no significant difference between the two β_2-agonists during either collection period. The longer duration of action of salmeterol over salbutamol cannot be explained in terms of any striking difference in effect on endogenous cysteinyl-leukotriene generation. This also suggests that β_2-adrenergic stimulation of the airway smooth muscle rather than the mast cell may be functionally more important in vivo.

The issue of salmeterol's putative anti-inflammatory effects in vivo is important but is not resolved by either Twentyman's study or ours. This will require more direct observation of other features of airway inflammation in asthma such as its effects on inflammatory cell influx and cell activation markers in bronchial biopsy specimens.

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SIR,—Your Dec 8 editorial misses the point of our study (Dec 1, p 1338) when it states that "Bronchodilatation lasted up to 9 hours, with protection against non-specific bronchial reactivity for up to 32 hours". Our study 1, in which no allergen was administered, showed that bronchodilatation and functional antagonism of bronchoconstriction did not extend to 32 hours after salmeterol administration. Study 2 then showed that salmeterol protected against the allergen-induced increase in bronchial responsiveness at 32 and 34 hours. This is an important point and implies that salmeterol has an additional action distinct from bronchodilatation and functional antagonism and can inhibit an effect of allergen that is normally associated with pulmonary inflammation and worsening asthma symptoms.[1]

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SIR,—Dr Twentyman and colleagues (Dec 1, p 1338), in their paper on the long-acting β-agonist salmeterol in asthma, interpret their data as showing a complete inhibition of both the early and late responses after allergen challenge. They base this claim upon the failure of antigen to cause significant bronchoconstriction when compared with a prechallenge baseline. However, in administering a potent and long-acting bronchodilator agent they have altered baseline forced expiratory volume (FEV_1) and histamine responsiveness such that the late response is only evident by comparison with a saline challenge. If this comparison is made, a late reaction is clearly demonstrated by changes in both airflow obstruction and histamine challenge, which parallel those after placebo. Salmeterol causes prolonged bronchodilation.[1] The fall in FEV_1 seen 3·5–9·5 h after allergen challenge is therefore surprising and provides further evidence that a late reponse is occurring. A similar decline in PC_{20} histamine of 2·2 doubling dilutions is seen between 1·5 and 7·5 h after challenge whereas there was apparently no significant change after saline control.

It is likely that salmeterol is causing long-acting functional antagonism of asthmatic responses because of its action at β_2-receptors. The parent compound, salbutamol, is not generally considered to be an anti-inflammatory agent,[2] although it prevents mast cell degranulation.[3] The suggestion that salmeterol may have a novel and as yet undetermined effect on the underlying inflammatory process in asthma should be treated with some caution. The claim that salmeterol has a potent anti-inflammatory action could lead to a dangerous decrease in steroid prescribing.

Salmeterol administration was associated with an improvement in FEV_1 and PC_{20} histamine 32 h post allergen challenge. This is the only tangible evidence of a true anti-inflammatory action. As Twentyman et al point out, stimulation of the β-receptor depends on the pharmacological profile of the drug used. Because of its uniquely long duration of action, simple comparison of salmeterol with conventional β-agonists is unjustified. Although modification of the late phase response may occur, it is misleading to claim its complete inhibition on the data presented in this study.

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Recurrence after first seizure

SIR,—The National General Practice Study of Epilepsy (Nov 24, p 1271) might leave the casual reader with the impression that the risk of recurrence after a first seizure is at least 78% within three years. The study group states that they have largely overcome selection bias but it is not clear how many patients were referred immediately after the first event.

The diagnosis "definite epileptic seizures" was made on all available information, including recurrence pattern, up to 6 months after the index seizure. What would have been the outcome in respect of accuracy of diagnosis and risk of recurrence if the diagnosis had been made immediately after the index seizure? Such a procedure would seem to be more relevant clinically.

Most patients had had several seizures (9% had had 10 or more) before they were enrolled. Including these patients (with a recurrence rate of 100%) in a study of the prognosis after a first seizure will certainly lead to gloomy results. The risk of recurrence for patients admitted after the first seizure (46%, group C) is of more practical importance, and accords with hospital-based studies.[1,2]

This study is of great importance for the epidemiology of epilepsy but application to clinical practice—for example, on the dilemma whether or not to start antiepileptic drug treatment after a first seizure—seems hazardous. The risk of recurrence in patients seen with a first seizure by a general practitioner or referred to a hospital will probably be far lower than 78%.

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