Calcium antagonists in exercise-induced asthma

SIR,—The report by Dr K R Patel (21 March, p 932) that the calcium antagonist verapamil inhibits exercise-induced asthma is supported by the observations of Cerrina and co-workers,¹ who report that nifedipine, another antagonist of calcium influx, also prevents the bronchoconstrictor response to exercise in asthmatics. In discussing the mechanism of exercise-induced asthma both Dr Patel and Cerrina *et al* suggest that the release of spasmogens from lung mast cells may play a role in this condition and that calcium antagonists, in addition to relaxing smooth muscle, may prevent exercise-induced bronchospasm by inhibiting the calcium-dependent release of these spasmogens.

In recent studies on the antigen-induced release of spasmogens from sensitised fragments of human lung, using well-established techniques,² we have confirmed that there is an absolute requirement for extracellular calcium ions in the release processes. However, nifedipine and verapamil at concentrations up to 100 $\mu\text{mol/l}$ failed to inhibit the release of histamine from human lung when the drug was preincubated with the tissue for 30 minutes before challenge. We did observe, however, that verapamil at 100 $\mu\text{mol/l}$, but not at 10 $\mu\text{mol/l}$, inhibited the release of slow-reacting substance. In addition, verapamil (500 pmol/l –150 $\mu\text{mol/l}$) inhibited the spasmogenic effect of histamine (1 $\mu\text{g/ml}$) on human superfused bronchial smooth muscle with a concentration effective in 50% of cases (EC_{50}) of 9 $\mu\text{mol/l}$.

Spasmogens derived from mast cells are unlikely to make a major contribution to the bronchoconstrictor response to exercise in asthmatics.³ Even if their contribution is greater than currently believed the results presented here suggest that calcium antagonists exert their inhibitory effects in exercise-induced asthma on the constrictor responses of bronchial smooth muscle rather than on the release of spasmogens from mast cells.

Nifedipine was a gift from Bayer UK Limited and verapamil was a gift from Abbott Laboratories Limited.

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¹ Cerrina J, Denjean A, Alexandre G, Lockhart A, Duroux P. *Am Rev Resp Dis* 1981;123:156-60.

² Butchers PR, Fullarton JR, Skidmore IF, Thompson LE, Vardey CJ, Wheeldon A. *Br J Pharmacol* 1979;67:23-32.

³ Deal EC, Wasserman SI, Soter NA, Ingram RH, McFadden ER. *J Clin Invest* 1980;65:659-65.

Are fibre supplements really necessary in diverticular disease of the colon?

SIR,—What should we do when clinical impressions over a number of years are not confirmed by a randomised, cross-over, double-blind controlled trial? With only an occasional exception patients with symptomatic uncomplicated diverticular disease of the colon report a persisting improvement when they take extra dietary fibre, often without an additional bulking agent. Personally I accept the verdict of my patients and then look doubly carefully at the double-blind trial.

The trial which you report by Mr M H Ornstein and others (25 April, p 1353) surely has an obvious fallacy. I was taught that the dose of a drug is that which has the desired effect without causing side effects, and the same is true for dietary supplements. To give a standard amount, and a small one at that, to every patient irrespective of their real need invites statistical disaster. In their subsequent letter (16 May, p 1629) the authors admit that "it is important to give sufficient bran or ispaghula to relieve straining and the amount will vary greatly between patients." This is equally true for other symptoms. With their own words they themselves condemn their own trial, which I believe is meaningless and dangerously misleading, although it appears to be beautifully designed and executed.

I am not alone in thinking that this paper should have been published in a specialist and not a leading world medical journal. This is not the first time that a clinical trial has given a dubious answer and I greatly welcome the article in your new series "Statistics in Question" about assessing clinical trials (16 May, p 1605).

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SIR,—It is regrettable that Mr M H Ornstein and others (25 April, p 1353), after carrying out an extensive clinical trial, have subsequently appeared to misinterpret their results. They have demonstrated that increasing the fibre intake of their patients with diverticular disease by 4.6 g was inadequate to produce sufficient relief of symptoms to reach levels of statistical significance, although the lowest mean symptom scores for pain, bowel symptoms, and general symptoms were seen when patients were taking bran. An increase of mean stool weight of less than 20 g daily and an increase in stool frequency from 9.55 to 10.34 per week may be inadequate to produce the desired effect on colonic behaviour.

I have found in clinical practice that symptomatic relief in diverticular disease is best achieved by increasing fibre intake by 20 g. This more than doubles the total fibre intake of most patients and almost invariably has a marked effect on bowel habit. Although patients will tolerate only a limited amount of bran, as Mr Ornstein and others state (16 May, p 1629), they will tolerate a much greater increase in fibre intake in the form of wholemeal bread, high-fibre breakfast cereals, etc.

A direct comparison has been made between this trial and a similar trial in Oxford.¹ The differences in results are difficult to explain, but could have been due to differences in the patients selected for the trials. Those at Oxford were all suffering from severe symptoms and all had abdominal pain in addition to bowel symptoms. The initial fibre intake of the patients may have been different. Differences in scoring techniques may have been important in the assessment of true differences in scores. In the previous trial a cross-over design was deliberately not used. The effect of altering fibre intake on bowel behaviour may persist for some months, in which case cross-over studies are inappropriate.

In the Oxford trial patients took the crispbread instead of bread, so that the placebo group had no increase in their normal fibre intake. In the present trial the control group did, in fact, have an increased fibre intake, according to Mr Ornstein and his colleagues

(p 1629), and it could be argued that there was no valid control group—only three different treatment groups.

The main value of this study has been to emphasise that small differences in fibre intake (equivalent to a small 50-g (1½-oz) packet of peanuts daily) may not be effective in treating diverticular disease. The recommended intake of many proprietary "bran" preparations is totally inadequate. Many gastroenterological and surgical clinics have found that a high-fibre diet (that is, 40 g a day—not 22 g as in this study) is effective in treating diverticular disease, but the optimal increase in dietary fibre required remains to be established scientifically.

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¹ Brodribb AJM. *Lancet* 1977;i:664-6.

SIR,—Despite the spirited criticism of Dr J R Thornton, Mr R T Burkitt, and Dr K O A Vickery (9 May, p 1546), it was unrealistic to have expected Mr M H Ornstein and his colleagues to retract the conclusions of their paper (25 April, p 1353)—namely, that dietary fibre supplements "do no more than relieve constipation" and "are unnecessary in the long-term management of uncomplicated diverticular disease." As it stands, however, their paper will undoubtedly be misquoted as its finer points become clouded by the passage of time. It is simply not enough for the authors to suggest subsequently (16 May, p 1629) that they made no claims concerning prevention of the disease; the fact that they neither mentioned this in their paper nor pointed out the total lack of other trial data relating to prophylaxis represents an important omission from their original and otherwise useful contribution.

Mr Ornstein and his colleagues are quite right in saying that a trial to test the lifelong prophylactic effect of fibre is impossible; a more realistic yet equally important question and, incidentally, one which they are in a prime position to tackle is: "Do fibre supplements, when given *long term* to patients with uncomplicated diverticular disease, prevent progression to the more serious stages of this common condition?" If the trial is explained, patients' co-operation should be no more of a problem in a trial to answer this question than, say, in a trial of antihypertensive therapy in the prevention of myocardial infarction or stroke.

It is a shame that the *Index Medicus* does not link original papers with the correspondence that they generate, for this might help to rectify sweeping overstatement by authors and prevent uncritical overinterpretation by readers. This paper and the constructive ensuing debate are a fair example of this problem.

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Multiple sclerosis

SIR,—Your leading article on multiple sclerosis (14 February, p 502) suggests that in a cross-sectional survey the median duration of the disease can be calculated by doubling the time from onset to prevalence day. The fallacy of this statement can be demonstrated with an extreme but simple example.

Suppose that 80% of patients with a particular disease survive for six months after