LETTERS TO THE EDITOR

Role of histamine release in hypertonic saline induced bronchoconstriction

In a recent study Dr O'Hickey and his colleagues (August 1989;44:650-3) investigated the inhibitory effect of terfenadine on hypertonic saline induced bronchoconstriction in asthmatic subjects. Terfenadine was administered in two doses of 120 mg 12 hours and two hours before challenge with hypertonic saline, and gave significant protection against this stimulus, displacing the geometric mean PD₂₀ FEV₁ from 22 to 56 l drawn from the ultrasonic nebuliser.

The authors concluded that airway histamine release was only one of several mechanisms mediating the bronchoconstrictor response to hypertonic saline, because of the substantial intersubject variation in the inhibitory effect of terfenadine in their study. This apparent heterogeneity may be due, among other factors, to an inadequate dose of terfenadine. Previous work, by Hopp *et al*, showed that when terfenadine was administered four hours before bronchial challenge with ultrasonically nebulized distilled water a drug dose of 240 mg gave better protection than that afforded by 120 mg.¹ A recent study using a dose of 180 mg terfenadine administered three hours before hypertonic saline challenge showed a geometric mean increase of PD₂₅ by a factor of 7.2,³ somewhat greater than the 2.5 fold shift reported by Dr O'Hickey and colleagues. It may be supposed that after airway mast cell degranulation a histamine concentration gradient exists, being highest close to the discharging cell, so that local histamine concentrations are higher than those encountered during inhaled histamine challenge. Thus doses of a competitive antihistamine apparently effective against inhaled histamine may be insufficient to overcome high local histamine concentrations. Moreover, although previous workers have demonstrated a dose related inhibition of histamine induced bronchoconstriction, using terfenadine in doses of 60, 120, and 180 mg, the displacement of the dose-response curve varied substantially between subjects.³ Both the variable efficacy of terfenadine and the intrinsic variability of ultrasonic saline challenge (the repeatability of which is not quantified in this study) may account for the apparently variable contribution of histamine to hypertonic saline induced bronchoconstriction reported by Dr O'Hickey and his associates.

JP FINNERTY
Medicine 1,
Southampton General Hospital,
Southampton SO9 4XY

- Hopp RJ, Bewtra K, Nair NM, Townley RG. Effect of terfenadine on the bronchoconstriction induced by ultrasonically nebulized distilled water. *Ann Allergy* 1988;61:13-6.
- Finnerty JP, Wilmot C, Holgate ST. Inhibition of hypertonic saline-induced bronchoconstriction by terfenadine and flurbiprofen: evidence for the predominant role of histamine. *Am Rev Respir Dis* (in press).
- Rafferty P, Holgate ST. Terfenadine (Seldane) is a potent and selective histamine H₁ receptor antagonist in asthmatic airways. *Am Rev Respir Dis* 1987;135:181-4.

AUTHOR'S REPLY We are pleased that Dr Finnerty found our article interesting and worthy of further comment. He suggests that the variable response observed was due to an inadequate dosage of antihistamine.

We do not believe that this is so because, in three out of the four subjects who had no protective effect from terfenadine on hypertonic saline induced bronchoconstriction, the same dosage of terfenadine induced a > 2, 13.8, and 16 fold reduction in histamine responsiveness. One subject declined further airway challenge. Thus the data indicate that the dose of terfenadine used was adequate to attenuate histamine responsiveness significantly, and further suggest a role for other mechanisms in hypertonic saline induced bronchoconstriction.

This hypothesis is supported both by the work of Silber *et al*,¹ who have shown that hyperosmolar nasal challenges induce the release of histamine, TAME esterase, and immunoreactive leukotrienes LTC₄, LTD₄, and LTE₄ into the nasal fluid, and that of Wilmot *et al*,² who have shown that pretreatment with the cyclooxygenase inhibitor flurbiprofen will attenuate hypertonic saline responsiveness in asthmatic subjects, suggesting a role for prostaglandins in the bronchoconstrictor response.

SP O'HICKEY
Department of Allergy and
Allied Respiratory Disorders,
Guy's Hospital,
London SE1 9RT

- Silber G, Proud D, Warner J, *et al*. In vivo release of inflammatory mediators by hyperosmolar solutions. *Am Rev Respir Dis* 1988;137:606-12.
- Wilmot C, Finnerty JP, Holgate ST. Role of histamine and prostaglandins in the bronchial response to inhaled hypertonic saline [abstract]. *Thorax* 1988;43:865P.

Fall in peak expiratory flow during haemodialysis in patients with chronic renal failure

The occurrence of allergic manifestations¹ and hypoxaemia² in patients undergoing haemodialysis using a new cuprophane membrane is well known. A study by Drs A Davenport and AJ Williams (September 1988;43:693-6) linked the fall in peak expiratory flow (PEF) with dialysis induced hypoxaemia and has suggested that bronchoconstriction which occurs as a result of the poor biocompatibility of a new cuprophane dialysis membrane may be contributory.

We have studied the PEF of 12 patients undergoing haemodialysis using dialysate buffered with acetate and a new cuprophane membrane produced by two manufacturers (Terumo Clirans model TAF 08, Sede Secondaria, Rome, and Gambro Alwall, Takanaawa, Minato-ku, Tokyo). Patients with underlying lung or autoimmune diseases and

those who were having immunosuppressive treatment were excluded. All patients were familiarised with the use of the peak flow meter before study and the best of three attempts were used for analysis. As shown in the table, a slight reduction of the PEF was observed after haemodialysis but the change was small and was not confined to the early period of dialysis, when hypoxaemia is known to occur.² We therefore could not confirm the findings of Drs Davenport and Williams. Our results suggest that significant bronchoconstriction does not occur after haemodialysis with a new cuprophane dialysis membrane and that the cause of hypoxaemia is more likely to be alveolar hypoventilation secondary to carbon dioxide washout or ventilation-perfusion disturbances produced by leucocyte sequestration in pulmonary capillaries, as previously suggested.²

PG WU
IKP CHENG
WK LAM
Department of Medicine,
University of Hong Kong,
Queen Mary Hospital,
Pokfulam,
Hong Kong

- Pollack VE, Charoenpanich R, Robson M, Kant KS. Dialyser membranes: syndromes associated with first use and effects of multiple use. *Kidney Int* 1988;33(suppl 24):S49-52.
- De Broe ME, Heyman RM, De Backer WA, Verpooten GS, Vermeire PA. Pathogenesis of dialysis-induced hypoxemia: a short overview. *Kidney Int* 1988;33(suppl 24):S57-61.

AUTHORS' REPLY Biocompatibility is a measure of the reaction that occurs when blood is passed through an extracorporeal circuit and returned to the patient. This reaction depends on the type of dialyser used, in terms of both the basic chemical structure and the method of manufacture of the membrane, its surface area, and the mechanics of haemodialysis; the blood and dialysate flow rates; and the chemical composition of dialysate used.

The study performed by Dr Wu and colleagues showed that when patients were dialysed with the Terumo reconstituted cellulose dialyser a significant reduction in PEF was observed during the first hour of dialysis. Thus they have confirmed our findings in a much smaller study using a dialyser with a smaller surface area. When they used a different cellulose based dialyser, however, no reduction in PEF was noted. This may reflect either a type 2 statistical error due to the small number of patients studied or differences in patient characteristics between the two dialysis treatments, such as the amount of fluid required to be removed during treatment, the blood flow, and the ultrafiltration rates. If changes in these measures could be excluded then it would be logical to explain the differences observed between the two dialysis treatments as reflecting differences in membrane biocompatibility.

Serial mean (SD) peak expiratory flow in patients undergoing haemodialysis using a new cuprophane dialysis membrane

Dialysis manufacturer	Time (min) from onset of dialysis						
	0	15	30	45	60	120	180
Terumo (TAF 08)	444 (68)	431* (60)	431* (64)	427* (62)	433 (63)	431 (59)	440 (68)
Gambro (ALWALL)	439 (56)	436 (55)	436 (53)	438 (52)	443 (54)	441 (54)	440 (53)
							447 (55)
							446 (52)

*p < 0.05 versus value at 0 time.

patibility. The temporal relation in the fall in PEF and arterial oxygen tension during haemodialysis, confirmed by Dr Wu and his colleagues, supports our initial contention that changes in PEF may be due to the activation of inflammatory mediators consequent on the activation of complement, neutrophils, monocytes, and platelets after the blood-dialyser interaction, resulting in an increase in pulmonary arteriolar tone and ventilation-perfusion mismatch and a reduction in tissue oxygen delivery.¹ This is supported by data obtained during the reuse of cuprophane dialysers, when the expected fall in PEF² and arterial oxygen tension and increase in platelet activation were much less than when the dialyser was used the first time.³

AJ WILLIAMS
A DAVENPORT

Department of Renal Medicine,
St James's University Hospital,
Leeds LS9 7TF

- 1 Henderson LW, Chenoworth D. Biocompatibility of artificial organs: an overview. *Blood Purif* 1987;5:100-1.
- 2 Williams AJ, Davenport A. Fall in peak expiratory flow during haemodialysis in patients with chronic renal failure. *Thorax* 1989;44:159.
- 3 Davenport A, Ahmad R. The effect of reuse of cuprophane dialysers on dialysis induced leukopenia and thrombocytopenia. *Dial Transplant* 1988;17:132-4.

Topical nasal anaesthesia for fiberoptic bronchoscopy

We would strongly support the conclusion of Dr AR Webb and others (August 1989;44:674-5) that lignocaine gel is preferable to lignocaine spray as a topical nasal anaesthetic for fiberoptic bronchoscopy. We suspect that any physician who has applied both agents to his own nostrils would agree with this suggestion as the spray preparation tends to cause an unpleasant stinging sensation when it comes in contact with the nasal mucosa. We have used lignocaine gel for many hundreds of bronchoscopic procedures with few complaints of discomfort from patients.

The technique which the authors used to apply the gel to the nose does, however, seem somewhat laborious. Although the revised technique described in the discussion section of the paper is more convenient than that used in the trial, we can recommend an alternative technique for gel application which we have found to be both convenient and effective.

We use a 12.5 cm hollow plastic applicator (Everett, Kwill) to draw up 10 ml of lignocaine gel from its tube into a syringe. The same applicator is then used to inject 5 ml of gel into each nostril. The 4 mm diameter applicator can easily be advanced to any desired depth within the nasal cavity, whereas the conical applicator on the tube of lignocaine will barely enter the anterior nares. We ask the patient to sniff, while occluding the opposite nostril, as the gel is applied, and we find that some of the gel is drawn into the pharynx, where it seems to provide useful preliminary topical anaesthesia before the introduction of the bronchoscope.

BR O'DRISCOLL
Chest Clinic, Wythenshawe Hospital,
Manchester M23 9LT

JR WEBB
Regional Respiratory Laboratory,
Brook General Hospital,
London SE18 4LW

We were interested to read the article by Dr AR Webb and others (August 1989;44:674-5) showing patients' preference for lignocaine gel over lignocaine aerosol for topical nasal anaesthesia preceding fiberoptic bronchoscopy. Seven years ago we reported the same preference for lignocaine gel by patients and normal subjects.¹ Nasal anaesthesia was equally effective with these two different methods, but the use of the aerosol was often associated with considerable nasal discomfort, an unpleasant taste, and epiphora, which did not occur with the gel. The additional advantage of the lubricating effect of the gel in passing the bronchoscope noted by Dr Webb and colleagues was also reported in our study. Furthermore, in our study plasma lignocaine concentrations were also measured to evaluate the safety of these different methods of administering lignocaine in both patients and a group of 10 normal subjects. Plasma lignocaine concentrations were lower after the same dose of lignocaine gel by comparison with the aerosol, suggesting that the gel might also be safer in terms of lignocaine toxicity.

JOHN EFTHIMIOU
Osler Chest Unit,
Churchill Hospital,
Oxford OX3 7LJ

TIM HIGENBOTTAM
Respiratory Physiology Department,
Papworth Hospital,
Papworth Everard,
Cambridge

- 1 Efthimiou J, Higenbottam T, Holt D. Plasma concentrations of lignocaine during fiberoptic bronchoscopy. *Thorax* 1982;37:68-71.

AUTHORS' REPLY We agree with Drs O'Driscoll and Webb that users of lignocaine gel for topical nasal anaesthesia may develop their own techniques for applying the gel. Indeed, some bronchoscopists in our own unit use a syringe based method similar to the one they describe. The technique documented in our recent publication has, however, been misinterpreted. The same technique is documented in both the "Methods" and the "Discussion" sections; it is the detail which is different in the two sections. We can assure readers that it is no more laborious to inject the gel from tube to nostril and massage it posteriorly than it is to open a syringe and Everett Kwill, draw the gel from the tube to the syringe, and then inject. It is also a little cheaper and, as our data show, provides effective topical anaesthesia.

We are grateful to Drs Efthimiou and Higenbottam for bringing their paper to our attention. The peak plasma lignocaine concentration in the nine patients given gel was reported to be not significantly less than the concentration in the 32 patients given lignocaine spray, though a lower peak plasma concentration was noted in volunteers given lower dosages of spray and gel. Thus lignocaine gel is at least as safe as lignocaine spray. These authors suggested a preference by patients for the gel in the discussion of their paper, and we have now measured the preference with a randomised study focusing on acceptability to patients.

AR WEBB
FJC MILLARD
St George's Hospital,
London SW17 0QT

Disturbance in respiratory mechanics in infants with bronchiolitis

I have read the report by Dr J Seidenberg and others (August 1989;44:660-7) on lung function in infants with bronchiolitis with considerable interest given our own studies in this field.¹ Whereas their results relating to forced and passive expiratory flow are certainly in line with what we expect in this obstructive lung disease, it appears that they, like us,¹ are in fact finding surprisingly low values for thoracic gas volume (TGV). It is true that in the acute phase their average TGV was 130% of predicted and in the chronic phase 126% of predicted, but the scatter was wide (see their SEM values) and several infants must have had values in or below their normal range. In our study in the chronic phase we noted many infants with TGV values below our normal range,² which is somewhat higher than the normal range used by Dr Seidenberg and his colleagues. Given the differences in normal range I suspect that the two studies contain an appreciable number of bronchiolitic infants with surprisingly low TGV values. They do not really come to grips with the thorny problem of whether or not TGV measurements are reliable in bronchiolitis. How, for example, do they know that all their values (both the high and the low) in the acute and chronic phases are not underestimated? I was delighted to see their results, which seem to confirm our own anxieties and suggest that our results were not simply an artefact. I should be most interested in their further thoughts on this issue.

S GODFREY
Department of Pediatrics,
Hadassah University Hospital,
Mount Scopus,
Jerusalem

- 1 Godfrey S, Beardsmore CS, Maayan Ch, Bar-Yishay E. Can thoracic gas volume be measured in infants with airways obstruction? *Am Rev Respir Dis* 1986;133:245-51.
- 2 Quanjer PH, Stocks J, Polgar G, Wise M, Karlberg J, Barsboom B. Compilation of reference values for lung function measurements in children. *Eur Respir J* 1989;2(suppl 4):184-261S.

Adverse effect of additional weight on exercise against gravity in patients with chronic obstructive airways disease

The conclusions of Dr C R Swinburn and others (September 1989;44:716-20) can be derived from common sense and an elementary knowledge of physics.

Acceleration or deceleration of a mass requires a force. If the mass is increased, a greater force is needed for the same acceleration. Alternatively, if the force is unchanged, less acceleration is produced ($\text{force} = \text{mass} \times \text{acceleration}$). In man the force is produced by muscle contraction, which uses energy. The energy is proportional to the force produced. When one walks at a steady pace, the legs alternately accelerate and decelerate but the body does not. Therefore the wearing of lead aprons will not substantially increase energy requirements, unless they are worn on the legs, not the thorax. Clearly, in step testing the whole body accelerates and decelerates in a vertical plane against gravity. So the wearing of lead aprons will make a difference to energy expenditure and hence oxygen consumption during this form of exercise.