EFFECTS OF TERBUTALINE SULPHATE AEROSOL ON BRONCHODILATOR RESPONSE AND LUNG MUCOCILIARY CLEARANCE IN PATIENTS WITH MILD STABLE ASTHMA

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1 Ventilatory function and whole lung mucociliary clearance have been assessed in 10 patients with mild stable asthma following inhalation of 1 mg of the β -adrenergic receptor agonist terbutaline sulphate (Bricanyl, Astra Pharmaceuticals) from a metered dose inhaler (MDI).

2 Compared to placebo inhalation, terbutaline produced marked bronchodilatation (mean percentage increase in FEV₁ 14%, $P < 0.01$).

3 Mucociliary clearance (measured by the *in vivo* radioaerosol technique) was assessed on three occasions—control, followed by placebo or terbutaline studies in a double-blind, cross-over manner.

4 Particles were removed from the lung at a similar rate in all three studies. The mean ($\pm$ s.e. mean) percentage of aerosol retained in the lungs after 6 h was $58 \pm 5\%$, $57 \pm 5\%$ and $57 \pm 4\%$ for control, placebo and drug studies respectively.

5 It is concluded that terbutaline sulphate, given as a 1 mg acute dose, does not enhance mucociliary clearance in mild stable asthmatics, although it produces marked bronchodilatation.

Introduction

β -adrenergic receptor agonists are intended primarily to relieve bronchospasm in patients with reversible airways obstruction. These substances may have valuable additional effects however, including inhibition of mediator release (Sörenby, 1975) and the enhancement of mucus transport. Terbutaline sulphate is a typical β -adrenoceptor agonist in that it has a powerful bronchodilator action when given by a variety of routes (Freedman, 1971; Koch, 1972; Michaelson *et al.*, 1978). It selectively stimulates β_2 -adrenoceptors in the bronchial tree, whilst having little or no effect upon cardiac β_1 -adrenoceptors. Terbutaline enhances tracheal mucus velocity when given subcutaneously to patients with airways obstruction (Mossberg *et al.*, 1976a; 1976b) and to healthy subjects (Camner *et al.*, 1976). However, the effect of terbutaline on mucus transport when administered via a pressurized metered dose inhaler (MDI) is largely unknown. We have investigated the acute effects upon both bronchodilator response and lung mucociliary clearance of a 1 mg dose of terbutaline sulphate, given from an MDI to patients with mild stable asthma.

Methods

Study design

Ten patients (six male, four female) clinically diagnosed as having mild stable asthma were investigated. All patients had demonstrated previously an increase of $\geq 15\%$ in the forced expiratory volume in 1 second (FEV₁) following bronchodilator inhalation. All were taking bronchodilator aerosols on a regular basis, but none was taking oral or inhaled corticosteroids. The mean age of the patients was 44 (s.e. mean 5) years; the mean weight 79 (s.e. mean 4) kg and the mean height 1.69 (s.e. mean 0.03) metres. Mean ($\pm$ s.e. mean) tobacco consumption was 19 ± 6 pack-years. Two patients were non-smokers, five ex-smokers and three current smokers.

In all, each patient performed five studies on five separate days at least 48 h but not more than 1 week apart. In the first two studies, bronchodilator response to either 1 mg terbutaline sulphate aerosol (Bricanyl, Astra Pharmaceuticals) or placebo aerosol was assessed in a double-blind cross-over manner. Five of the patients were given terbutaline and five patients given placebo during the first of these two studies. Mucociliary clearance was measured during the third, fourth and fifth studies. In the third study, a control mucociliary clearance measurement was performed.

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In the fourth and fifth studies mucociliary clearance was assessed following administration of either 1 mg terbutaline sulphate aerosol (Bricanyl, Astra Pharmaceuticals) or placebo aerosol in a double-blind cross-over manner. Patients refrained from taking their prescribed bronchodilators for 12 h prior to commencement of all studies, for the duration of the bronchodilator response studies and during the initial 6 h recording period in mucociliary clearance studies.

All patients gave informed consent in writing, and the investigations were approved both by the Ethical Practices Committee of the Hospital and the Radioisotope Advisory Panel of the Department of Health and Social Security.

Bronchodilator response studies

Patients inhaled either four puffs (1 mg) terbutaline sulphate aerosol or four puffs of placebo aerosol which consisted of chlorofluorocarbons 11, 12 and 114 with sorbitan trioleate surfactant (14 mg ml^{-1}) but no active drug particles. Bronchodilator response was assessed from simple spirometric tests. FEV₁ and forced vital capacity (FVC) were measured using a dry bellows spirometer (Vitalograph) and peak expiratory flow rate (PEFR) was measured using a Wright peak flow meter. These tests were performed prior to drug or placebo inhalation, and then 15, 30, 60 and 120 min later. Changes in maximal forced expiratory flow rate at 50% vital capacity ($V_{\max 50}$) were measured at 15 and 120 min post inhalation from maximal expiratory flow-volume curves using an Ohio 840 spirometer coupled to a Byrans X-Y plotter. The highest of three technically acceptable readings was recorded at each time for each lung function test.

Mucociliary clearance studies

Whole lung mucociliary clearance was assessed using the *in vivo* radioaerosol technique which has already been reported more fully elsewhere (Thomson & Short, 1969). Patients inhaled in a controlled manner particles of polystyrene, firmly labelled with the gamma-emitting isotope $^{99}\text{Tc}^m$. Inhalation, limited to a volume of 450 ml, commenced at functional residual capacity (FRC) and was followed by 3 s breath-holding to allow particles to settle onto the airways at their furthest point of penetration. Inhaled flow rate was monitored by a pneumotachygraph.

Immediately prior to radioaerosol inhalation, FEV₁, FVC and maximum mid-expiratory flow rate (MMEF) were assessed using a Vitalograph spirometer, and PEFR using a Wright peak flow meter. In the drug and placebo runs, four puffs of either terbutaline sulphate (Bricanyl, Astra Pharmaceuticals) or placebo were then administered from an MDI. The time interval between drug or placebo

administration and radioaerosol inhalation was approximately 1 min.

Immediately following radioaerosol inhalation, the initial topographical distribution of deposited particles in the right lung was measured using a rectilinear gamma scanner (Dawson *et al.*, 1971). The scanner recorded radioactivity in a series of vertical traverses of the right lung, each of width 2.5 cm. An aerosol penetration index (API) was calculated as the quantity of radioactivity detected over the peripheral two-fifths of the lung compared to that recorded over the inner two-fifths (Thomson *et al.*, 1975).

Clearance of particles from the lungs was recorded using two diametrically opposed scintillation probes, one located anteriorly over the midsternum, and the other location posteriorly. Counts emanating from the chest were recorded immediately after radioaerosol inhalation and then at hourly intervals for 6 h. These counts were corrected for background and radioactive decay. Patients returned after 24 h for a final measurement of chest radioactivity. The quantity of aerosol retained in the lungs after 24 h, corrected for background and radioactive decay, was taken to be alveolar deposition, on the assumption that those particles deposited on the conducting airways had been removed by mucociliary clearance and productive coughing by that time. The number of coughs and expectoration of sputum was recorded during the 6 h following radioaerosol inhalation.

Statistical analysis

The data were not assumed to be normally distributed, and statistical significance was assessed by non-parametric methods. The tests used were the Wilcoxon rank sum test for paired data and the Friedman analysis of variance by ranks (Siegel, 1956).

Results

Bronchodilator response studies

Inhalation of 1 mg terbutaline sulphate aerosol resulted in marked bronchodilatation in the 10 asthmatic subjects throughout the 2 h recording period. After 30 min, the mean ($\pm$ s.e. mean percentage change in FEV₁ was $14 \pm 3\%$ for terbutaline, and $-1 \pm 2\%$ for placebo ($P < 0.01$). Similar changes were noted for PEFR (drug $17 \pm 4\%$, placebo $0 \pm 2\%$, $P < 0.01$), and the change in FVC was also significantly ($P < 0.01$) enhanced after terbutaline inhalation. Changes in $V_{\max 50}$ after terbutaline inhalation were also greater than those after placebo inhalation, but these differences did not attain statistical significance. Baseline FEV₁ values were similar on the 2 study days, being 2.70 l (s.e. mean 0.34 l) on the terbutaline day and 2.86 l (s.e. mean 0.35 l) on the placebo day.

Mucociliary clearance studies

The clearance of radioactive particles from the lungs is shown in Figure 1. The quantity of radioactive particles remaining in the lungs is plotted against time as a percentage of the amount initially present. There were no significant differences between control, placebo and drug studies in the amount of aerosol retained in the lungs at any time up to 24 h after radioaerosol inhalation. After 6 h, the mean ($\pm$ s.e. mean) whole lung retention of radioaerosol was $58 \pm 5\%$, $57 \pm 5\%$ and $57 \pm 4\%$ for control, placebo and drug studies respectively. Mean ($\pm$ s.e. mean) alveolar deposition, as indicated by the 24 h whole lung retention, was $39 \pm 4\%$, $40 \pm 5\%$ and $44 \pm 6\%$ for the three studies. This indicated that mucociliary clearance was unaltered by terbutaline compared either to placebo or to the control study.

Figure 1 Acute effect of inhaled terbutaline sulphate (1 mg) on whole lung mucociliary clearance in 10 patients with mild stable asthma. Group mean retention of deposited radioaerosol in the whole lung is plotted as a percentage of the initial count. ■ control, ● placebo, ▲ terbutaline.

The data shown in Figure 1 were replotted by subtracting the 24 h retention of radioaerosol (alveolar deposition) and expressing the remaining radioactivity as tracheobronchial clearance (Figure 2). As in the case of whole lung clearance, there were no significant differences between control, placebo and drug studies. Tracheobronchial retention at 6 h was 32 ± 7 (mean $\pm$ s.e. mean)%, $28 \pm 7\%$ and $23 \pm 6\%$ respectively.

Ventilatory function, measured prior to radioaerosol inhalation was similar for each of the three clearance studies, there being no significant differences in FEV₁, FVC, PEFR and MMEF (Table 1). Flow rate of inhaled radioaerosol also varied little on each study day, being 27 ± 1 (mean $\pm$ s.e. mean) l min⁻¹, 27 ± 2 l min⁻¹ and 29 ± 2 l min⁻¹ for control, placebo and drug studies respectively. The number of coughs

Figure 2 Acute effect of inhaled terbutaline sulphate (1 mg) on tracheobronchial clearance in 10 patients with mild stable asthma. Group mean retention of deposited radioaerosol in tracheobronchial zones is plotted as a percentage of the initial count. ■ control, ● placebo, ▲ terbutaline.

and the volume of expectorated sputum did not vary significantly among the three studies (Table 2). The number of coughs was greatest in the placebo study, although the wet weight of sputum produced was least. Sputum was expectorated by two patients in control and drug studies and by only one patient in the placebo study.

The initial topographical distribution of radioaerosol in the lungs was expressed in terms of the aerosol penetration index (API). In the control study, API was 0.54 ± 0.05 (mean $\pm$ s.e. mean), but fell significantly to 0.34 ± 0.05 ($P < 0.01$) in the placebo study and to 0.43 ± 0.05 ($P < 0.02$) in the terbutaline study. This finding indicates a more central deposition pattern within the lungs for both placebo and drug studies. There was no significant difference between API in the placebo study and API in the drug study.

Table 1 Mean ($\pm$ s.e. mean) ventilatory function prior to radioaerosol inhalation in 10 patients with mild stable asthma. Mean percentage predicted values are shown in the parentheses.

	Control study	Placebo study	Terbutaline study
FEV ₁ (l)	2.86 ± 0.35 (90%)	2.76 ± 0.35 (87%)	2.93 ± 0.36 (92%)
FVC (l)	3.70 ± 0.45 (95%)	3.75 ± 0.44 (96%)	3.83 ± 0.45 (98%)
PEFR (l min ⁻¹)	427 ± 35 (86%)	423 ± 35 (85%)	438 ± 36 (88%)
MMEF (l s ⁻¹)	2.51 ± 0.43 (69%)	2.38 ± 0.47 (65%)	2.49 ± 0.40 (68%)

Table 2 Mean ($\pm$ s.e. mean) number of coughs and mean ($\pm$ s.e. mean) wet weight of sputum expectorated during first 6 h of mucociliary clearance studies in 10 mild stable asthmatics.

	Control study	Placebo study	Terbutaline study
Coughs	13 $\pm$ 5	29 $\pm$ 18	10 $\pm$ 2
Wet weight of sputum (g)	0.56 $\pm$ 0.50	0.12 $\pm$ 0.11	0.40 $\pm$ 0.27

Discussion

These investigations have shown that a 1 mg acute dose of terbutaline sulphate aerosol, given from an MDI, does not elicit an increase in mucociliary clearance in patients with mild stable asthma, even though this dose is sufficient to produce marked bronchodilator response. The standard dose of terbutaline aerosol is two puffs (500 μ g). Our findings are in agreement with those of a previous study from our laboratory (Pavia *et al.*, 1980a) in which the administration of two puffs of terbutaline four times daily for 1 week produced no enhancement of mucociliary clearance in patients with chronic bronchitis.

In the present studies, drug or placebo was administered immediately before radioaerosol inhalation, in order that any coughing associated with administration of drug or placebo should not result in removal of radioactive particles from the lungs. Compared to the control study, aerosol penetration was significantly reduced in drug and placebo studies, possibly because of an initial bronchoconstrictor effect as a result of inhaling chlorofluorocarbon propellants or surfactant. A transient bronchoconstrictor effect (duration approximately 1 min) was noted in asthmatic subjects who inhaled fenoterol aerosol (Nolte *et al.*, 1979). This effect was ascribed to the cold propellant spray, since it was reversed when the drug itself began to act. Sterling & Batten (1969) also noted transient bronchoconstriction (duration < 5 min) after inhalation of placebo pressurised aerosols. Since the time between terbutaline or placebo administration and radioaerosol inhalation was approximately 1 min in the present study, any bronchoconstriction produced by the metered dose aerosols might still have been present when the radioaerosol was inhaled. A reduced API suggests that radioaerosol deposition was shifted away from small airways towards larger, more central, airways in both placebo and drug studies. Alveolar deposition as assessed by the 24 h whole lung retention of radioaerosol, was similar for control, placebo and drug studies, however. No enhancement of the rate of mucus clearance was noted in the terbutaline study, even though the transit path of the radioactive

particles to the throat was presumably shorter than that in the control study, and similar to that in the placebo study.

Mucociliary clearance is impaired in subjects with obstructive airway disease (Pavia *et al.*, 1980b), even in patients with only mild asthma (Bateman *et al.*, 1979). Many β -adrenergic agents are capable of accelerating clearance in such patients towards more normal levels (Sackner, 1978). Salbutamol (Fazio & Laforuna, 1981) given from an MDI and clenbuterol (Weiss *et al.*, 1981) given orally, improve whole lung mucociliary clearance in subjects with chronic bronchitis, and tracheal mucus velocity may be increased in normal subjects by nebulized adrenaline and isoprenaline (Foster *et al.*, 1976) and by nebulized orciprenaline (Yeates *et al.*, 1981). Isoprenaline aerosol improves tracheal mucus velocity in anaesthetized dogs (Sackner *et al.*, 1976). Terbutaline, given subcutaneously in a dose of 250 μ g, was found to enhance lung mucociliary clearance in healthy subjects (Camner *et al.*, 1976), in asthmatics (Mossberg *et al.*, 1976a) and in chronic bronchitis with only moderate ventilatory impairment (Mossberg *et al.*, 1976b). The same dose of terbutaline given subcutaneously was found to enhance tracheal mucus velocity in patients with cystic fibrosis (Wood *et al.*, 1975) and chronic obstructive lung disease (Santa Cruz *et al.*, 1974) although not in normal subjects. Oral administration of 5 mg terbutaline enhanced the clearance of lung secretions both in bronchitic subjects and in healthy volunteers (Konietzko *et al.*, 1975).

To date, no study has demonstrated an enhancement of mucus clearance from terbutaline sulphate in aerosol form. Terbutaline (250 μ g) given subcutaneously appears to have a potent effect on mucus clearance in subjects with obstructive airways disease (Santa Cruz *et al.*, 1974; Wood *et al.*, 1975; Mossberg *et al.*, 1976a,b), but we did not find the same to be true of a 1 mg dose given as an aerosol. Our technique is, however, capable of detecting enhancement of clearance following administration of respiratory drugs. More rapid clearance has been noted in subjects with obstructive airway disease given the mucolytic bromhexine (Thomson *et al.*, 1974), hypertonic saline aerosol (Pavia *et al.*, 1978) and aminophylline (Sutton *et al.*, 1981). It is possible that the dose of terbutaline administered in the present study, although twice the normal therapeutic dose, was too low. The inhaled route is inefficient in its delivery of drug to the lung, since only about 10% of the aerosol dose reaches the airways (Newman *et al.*, 1981). Only 100 μ g of a 1 mg dose would therefore reach the bronchial tree, and the surface concentration of the drug particles on the airway mucosa would be correspondingly small, particularly in the peripheral regions of the lung. It is possible that terbutaline aerosol given in twice the normal therapeutic dose is insufficient to stimulate

mucus clearance, even though this dose is able to give marked bronchodilatation.

It is interesting to note that published studies which have demonstrated an enhancement of mucus transport following subcutaneous administration of terbutaline are those in which measurements were confined entirely or primarily to central lung zones. The technique used by Wood *et al.* (1975) and by Santa Cruz *et al.* (1974) involved the monitoring of opaque Teflon discs which had been previously introduced into the trachea, and tracheal mucus velocity was calculated from the rate of movement of the discs observed by X-ray screening. The technique employed by Camner *et al.* (1976) and by Mossberg *et al.* (1976a,b) involved the inhalation and subsequent clearance of 6 μm diameter Teflon particles. Teflon has a density of 2.1 g cm^{-3} so that the aerodynamic diameter of these particles was $6 \times \sqrt{2.1} \mu\text{m}$, i.e. 8.7 μm . Particles of this aerodynamic size are very susceptible to deposition in large central airways of the lungs (Lippman & Albert, 1969) and relatively few reach the more peripheral zones. Clearance of these particles therefore reflects chiefly mucus transport in large central airways. Our radioaerosol has an aerodynamic diameter of 5 μm , and is delivered more uniformly to the lungs, (on average 41% of the particles has not been cleared from the lungs after 24 h in these

studies), so that the mucociliary clearance measurement is averaged over both large and small conducting airways. If terbutaline enhances clearance in the most central airways only, then this might be more readily detected by methods which primarily assess clearance from these regions. Spektor *et al.* (1979) have reported that oral administration of 20 mg orciprenaline, another β -adrenoceptor agonist, enhanced tracheal mucus velocity in healthy non-smokers, but did not increase overall clearance of particles from the lungs. However, Sadoul *et al.* (1981), using a radioaerosol technique which monitored clearance primarily from large central airways, were unable to detect an increase in clearance in chronic bronchitic subjects given orally 7.5 mg terbutaline daily.

In conclusion therefore, terbutaline sulphate aerosol, given as twice as usual therapeutic dose, does not enhance whole lung mucociliary clearance in mild asthmatics, even though marked bronchodilatation was produced. The reason for this may well be dose-related, or may occur because terbutaline promotes clearance primarily in more central lung regions only. Further studies are indicated in order to investigate this problem further.

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References

- BATEMAN, J.R.M., PAVIA, D., SHEAHAN, N.F., AGNEW, J.E. & CLARKE, S.W. (1979). Tracheobronchial clearance in asthma. *Thorax*, **34**, 418.
- CAMNER, P., STRANDBERG, K. & PHILIPSON, K. (1976). Increased mucociliary transport by adrenergic stimulation. *Arch. Environ. Health*, **39**, 79–82.
- DAWSON, H., DOUGLAS, R.B., PAVIA, D., REEVES, E., SHORT, M.D. & THOMSON, M.L. (1971). *Phys. Med. Biol.*, **16**, 691–692.
- FAZIO F. & LAFORTUNA, C. (1981). Effect of salbutamol on mucociliary clearance in patients with chronic bronchitis. *Chest*, **80**, Supplement, 827–830.
- FOSTER, W.M., BERGOFSKY, E.H., BOHNING, D.E., LIPPMANN, M. & ALBERT, R.E. (1976). Effect of adrenergic agents and their mode of action on mucociliary clearance in man. *J. appl. Physiol.*, **41**, 146–152.
- FREEDMAN, B.J. (1971). Trial of a new bronchodilator, terbutaline, in asthma. *Br. med. J.*, **1**, 633–636.
- KOCH, G. (1972). Terbutaline in bronchial asthma. Effect on lung volumes, ventilatory performance, pulmonary gas exchange and circulation at rest and during exercise. *Scand. J. resp. Dis.*, **53**, 187–195.
- KONIEZKO, N., KLOPFER, M., ADAM, W.E. & MATTHYS, H. (1975). The influence of beta-adrenergic stimulation on the mucociliary system of the human lung. *Pneumologie*, **152**, 203–208.
- LIPPMANN, M. & ALBERT, R.E. (1969). The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. *Am. Ind. Hyg. Ass. J.*, **30**, 257–275.
- MICHAELSON, E.D., SILVA, G.T., FORREST, T.R., MARKS, M.B., SERAFINI, S.M. & SACKNER, M.A. (1978). Effects of oral terbutaline in children with bronchial asthma. *J. Allergy clin. Immunol.*, **61**, 365–369.
- MOSSBERG, B., STRANDBERG, K., PHILIPSON, K. & CAMNER, P. (1976a). Tracheobronchial clearance in bronchial asthma: response to beta-adrenoceptor stimulation. *Scand. J. resp. Dis.*, **57**, 119–128.
- MOSSBERG, B., STRANDBERG, K., PHILIPSON, K. & CAMNER, P. (1976b). Tracheobronchial clearance and beta-adrenoceptor stimulation in patients with chronic bronchitis. *Scand. J. resp. Dis.*, **57**, 281–289.
- NEWMAN, S.P., PAVIA, D., MOREN, F., SHEAHAN, N.F. & CLARKE, S.W. (1981). Deposition of pressurized aerosols in the human respiratory tract. *Thorax*, **36**, 52–55.
- NOLTE, D., BERGER, D. & FORSTER, E. (1979). Do metered aerosol propellants have a bronchoconstrictor effect? *Deutsche med. Wochenschrift*, **104**, 172–174.
- PAVIA, D., THOMSON, M.L. & CLARKE, S.W. (1978). Enhanced clearance of secretions from the human lung after administration of hypertonic saline aerosol. *Am. Rev. resp. Dis.*, **117**, 199–203.
- PAVIA, D., BATEMAN, J.R.M., SHEAHAN, N.F. & CLARKE, S.W. (1980a). Clearance of lung secretions in patients with chronic bronchitis: effect of terbutaline and ipratropium aerosol. *Eur. J. resp. Dis.*, **61**, 245–253.
- PAVIA, D., BATEMAN, J.R.M. & CLARKE, S.W. (1980b). Deposition and clearance of inhaled particles. *Bull. Eur. Physiopath. Resp.*, **16**, 335–366.

- SACKNER, M.A., EPSTEIN, S. & WANNER, A. (1976). Effect of beta-adrenergic agonists aerosolized by freon propellant on tracheal mucus velocity and cardiac output. *Chest*, **69**, 593-598.
- SACKNER, M.A. (1978). Effect of respiratory drugs on mucociliary clearance. *Chest*, **73**, 958-966.
- SADOUL, P., PUCHELLE, E., ZAHM, J.M., JACQUOT, J., AUG, F. & POLU, J.M. (1981). Effect of terbutaline on mucociliary transport and sputum properties in chronic bronchitis. *Chest*, **80**, Supplement, 885-889.
- SANTA CRUZ, R., LANDA, J., HIRSCH, J. & SACKNER, M.A. (1974). Tracheal mucus velocity in normal man and patients with obstructive lung disease: effects of terbutaline. *Am. Rev. resp. Dis.*, **109**, 458-463.
- SIEGEL, S. (1956). *Non-parametric statistics for the behavioural sciences*. Tokyo: McGraw-Hill Kogakusha.
- SÖRENBY, L. (1975). The beta-adrenoceptors of the lung mediating inhibition of antigen-induced histamine release. *Eur. J. Pharmac.*, **30**, 140-147.
- SPEKTOR, D.M., PITT, B.R. & YEATES, D.B. (1979). Changes in regional mucociliary transport in the human lung resulting from systemic beta-2 adrenergic stimulation. *Am. Rev. resp. Dis.*, **119**, 236.
- STERLING, G.M. & BATTEN, J.C. (1969). Effect of aerosol propellants and surfactants on airway resistance. *Thorax*, **24**, 228-231.
- SUTTON, P.P., PAVIA, D., BATEMAN, J.R.M. & CLARKE, S.W. (1981). The effect of oral aminophylline on lung mucociliary clearance in man. *Chest*, **80**, Supplement, 889-892.
- THOMSON, M.L. & SHORT, M.D. (1969). Mucociliary function in health, chronic obstructive airways disease and asbestosis. *J. appl. Physiol.*, **26**, 535-539.
- THOMSON, M.L., PAVIA, D., GREGG, I. & STARK, J.E. (1974). Bromhexine and mucociliary clearance in chronic bronchitis. *Br. J. dis. Chest*, **68**, 21-27.
- THOMSON, M.L., PAVIA, D., JONES, C.J. & McQUISTON, T.A.C. (1975). No demonstrable effect of S-carboxymethylcysteine on clearance of secretions from the human lung. *Thorax*, **30**, 669-673.
- WEISS, T., DOROW, P. & FELIX, R. (1981). Effects of a beta adrenergic drug and a secretolytic agent on regional mucociliary clearance in patients with C.O.L.D. *Chest*, **80**, Supplement, 881-885.
- WOOD, R.E., WANNER, A., HIRSCH, J. & FARRELL, P.M. (1975). Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. *Am. Rev. resp. Dis.*, **111**, 733-738.
- YEATES, D.B., SPEKTOR, D.M., LEIKAUF, G.D. & PITT, B.R. (1981). Effects of drugs on mucociliary transport in the trachea and bronchial airways. *Chest*, **80**, Supplement, 870-873.

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