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Editorial

# Therapeutic aerosols 1—Physical and practical considerations

The inhaled route is a logical means of treating respiratory disorders since drugs may be delivered directly to the large surface area of the tracheobronchial tree and alveoli. The value of inhalation treatment was recognised by ancient civilisations in India, China, and the Middle East, as well as by Hippocrates and Galen.[1] Since those times, and particularly recently, inhalation treatment has increased greatly in sophistication, and the advantages of this route for the delivery of specific drugs have become well recognised. The drugs often begin to act very rapidly, and as a smaller dose can be used than with oral or intravenous delivery there is generally a reduction in the incidence of systemic side effects.

This review is in two parts. This first part will discuss the physical nature of therapeutic aerosols and the importance of ensuring correct use of the various inhalation devices if aerosols are to reach their required site of action—so far as that is known. The second part will describe the wide range of drugs which may be given in aerosol form as topical treatment for pulmonary disorders and in some instances as a form of systemic treatment.

## Aerosol kinetics

An aerosol is a suspension of solid particles or liquid droplets in air. An important but often neglected aspect of the therapeutic use of aerosols is the fact that they are subject to the laws of aerosol kinetics. These laws govern deposition within the respiratory tract and are concerned principally with inertial impaction and gravitational sedimentation.[2] Other mechanisms, of which Brownian diffusion is the best known, are probably of little relevance for therapeutic aerosols, and will not be considered further.

Inertial impaction occurs chiefly with larger particles whenever the transporting airstream is fast, changing direction, or turbulent (for example, in the oropharynx or at bifurcations between successive airway generations). Inertial deposition therefore is confined mainly to the upper airways—nose, mouth, pharynx, and larynx—and large conducting airways of the lung down to 2 mm in diameter. Here the cross sectional area is small and the flow high.

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Gravitational sedimentation, by contrast, is a time dependent process in which small aerosol particles settle in airways under the effect of gravity, during either breath holding or slow tidal breathing. It takes place mainly in small airways (<2 mm diameter) and alveoli, where the rapid increase in cross sectional area gives low flows and where large particles will rarely penetrate. This combination of small particles in small airways with low flows gives time for the particles to sediment for the short distance required.

In general, most aerosol particles greater than 8 $\mu$m diameter will impact above the level of the larynx and will not reach the lung.[3] Particles of 1–8 $\mu$m may be deposited by impaction and sedimentation in both large and small airways and alveoli. Particles less than 1 $\mu$m diameter may not be deposited at all, many being respired like an insoluble gas. Of course, the overlap between particle sizes and area of deposition may be considerable.

## Factors affecting deposition

A wide range of other factors influences the deposition of aerosols within the respiratory tract. These can be conveniently divided into three categories: (*a*) mode of inhalation, (*b*) aerosol properties, and (*c*) factors relating to the patient.

### MODE OF INHALATION

The most important features of inhalation are the inhaled volume, the flow rate, and any breath holding pause maintained at end inspiration. The greater the inhaled volume the more peripherally the particles will be distributed in the lungs.[4] By contrast, as the inhaled flow rate is increased particles are more likely to be deposited in the oropharynx or in the large central airways of the lungs by inertial impaction.[4] A period of breath holding enhances deposition in the more peripheral parts of the lungs by gravitational sedimentation.[5]

### AEROSOL PROPERTIES

The vital physical property of the aerosol itself is the aerodynamic diameter (the product of physical diameter and the square root of density). Aerosol particle size may be measured by several techniques,

the best known of which are cascade impaction[6] and laser light scattering.[7] As the aerodynamic diameter increases from about 2 $\mu$m deposition in the oropharynx and large conducting airways becomes more likely, although less aerosol is exhaled and less reaches the most peripheral parts of the lung.[8,9] Therapeutic aerosols are usually heterodisperse—that is, they comprise particles of many different sizes—and their behaviour is probably best described by the mass median aerodynamic diameter (MMAD)[10]; half of the aerosol mass is contained in particles smaller and half of the aerosol mass in particles larger than the MMAD. The ideal size for a therapeutic aerosol is not known precisely but it may be assumed that the MMAD should be not more than 5 $\mu$m to penetrate into the tracheobronchial tree and smaller airways if peripheral deposition is required. Most therapeutic aerosols are hygroscopic, however, and the inhaled particles absorb water within the humid environment of the respiratory tract, subsequently enlarging in size, so that their aerodynamic behaviour is not fully understood.

### FACTORS RELATING TO THE PATIENT

There is a wide intersubject variability of aerosol deposition apparently related to random anatomical variations of airway geometry.[11] Particles of a given size inhaled during tidal breathing are more readily deposited in central lung zones in patients with airway obstruction, and fewer particles reach the lung periphery.[4,12,13] Thus the presence of airways obstruction is a major determinant of particle deposition, with one curious exception. Recent studies of single breath metered dose aerosol deposition have shown little or no relationship between those deposition patterns and the degree of airway obstruction,[14,15] suggesting that this type of aerosol can penetrate equally well to the lung periphery in patients with both mild and severe airway obstruction.

## Types of inhalation device

How do these considerations apply to aerosols released from the various types of inhalation device used for treatment? There are three types of device in common use—the metered dose inhaler (MDI), the dry powder inhaler, and the nebuliser—and each will be considered in turn.

### METERED DOSE INHALER

Metered dose aerosols may be formulated either as suspensions of fine drug crystals or as drug solutions mixed with chlorofluorocarbon propellants. In either case the propellant droplet size, rather than the drug particle or droplet size, may influence the site of deposition.

The propellants have a high vapour pressure of about 400 kPa keeping them in the liquid phase within the canister. When the aerosol is actuated, the contents of a small metering chamber are released with rapid, initial vaporisation of propellant, often called "flashing." This breaks up the liquid stream into droplets, which may typically have an MMAD exceeding 35 $\mu$m at the actuator orifice.[16] Particle size reduces to 14 $\mu$m at a distance of 10 cm and is only marginally less at 25 cm from the canister. The propellant droplet velocity may initially exceed 30 m per second (the legal motorway speed!).

The particle size and velocity of the aerosol ensure that, although the MDI is compact and portable, contains several hundred doses, and is apparently easy to use, only about 10% of the dose reaches the lungs.[17] Most of the particles impact in the oropharynx.

Matters are often made worse by failure on the part of the patients to use the MDI properly. The incidence of inhaler misuse is high,[18] and this may be due at least in part to the differing and rather confusing instructions issued to patients in manufacturers' leaflets. The most important error is failure to coordinate firing the MDI with inhaling (often called a "hand lung" problem), since patients must time their inhalation correctly in order to "catch" the rapidly moving bolus of aerosol.[19] Many patients stop inhaling at the moment the aerosol spray is released, in reaction to the cold propellant spray hitting the back of the mouth.[19] Other patients inhale too quickly, or fail to breath hold adequately.[18] Unfortunately, inadequate knowledge about good inhaler technique is not confined to patients—a high proportion of physicians, nurses, and pharmacists may be unable to use an MDI correctly.[20,21] Thus it is likely that many patients use their MDIs incorrectly because of poor advice.

The optimal mode of inhalation, which maximises both aerosol delivery to the lungs as assessed by radiotracer techniques[22] and bronchodilator response to a metered dose inhaler,[23] has recently been explored. This mode involves two vital features: firstly, firing the MDI during a slow, steady inhalation and, secondly, following this with a period of 10 seconds' breath holding (or if less for as long as possible). Slow inhalation reduces impaction losses in the upper airways, and breath holding allows those particles which reach the lung periphery to settle on to the airways under gravity. Both these features are essential. The bronchodilator response may not be enhanced by slow inhalation unless the patient holds his breath for 10 seconds,[24] and bronchodilatation may not be enhanced by breath holding unless the patient

inhales slowly.[25] Even with this optimal technique (termed the "10 second rule"), no more than about 15% of the available dose reaches the lungs. This method is simple and well within the compass of most patients. There are some, however, who will never master the technique, and who should be given treatment with alternative types of inhalation device.

It should be noted that the lung volume at which aerosol is released and the subsequent inspired volume of air are both relatively unimportant, provided that inhaled flow rate and breath holding are optimal. A delay of about 15 minutes between successive doses of bronchodilator is often advocated, to allow the first dose to act before the next dose is given.[26] Not all studies, however, have found this approach beneficial,[27] and since it makes treatment rather more complicated it may reduce the patient's compliance. It seems preferable to recommend an interval of about one minute between successive doses—long enough to let the actuator nozzle and valve stem warm up from the sudden temperature drop (~15°C) that occurs each time the inhaler is fired. Theoretically, successive firing may progressively reduce the temperature of the spray, though in practice there is no evidence that this matters. A recent study[28] found comparable effects whether bronchodilator and corticosteroid doses were spaced 30 seconds or 7–8 minutes apart, suggesting that the longer interval between doses did not enhance drug penetration.

An "open mouth" MDI technique has been advocated—in which the inhaler is held 3–5 cm from the open mouth or between the open lips. While this technique should reduce oropharyngeal losses of drug, and has been shown to enhance therapeutic effect,[29] it cannot be recommended for general use as the spray may well miss the mouth entirely. Pointing the inhaler upwards on to the roof of the mouth or downwards on to the tongue are further common errors to be avoided. To help patients with coordination problems, breath actuated MDIs have been introduced in which the patient's inhalation triggers a spring mechanism which fires the inhaler. These devices tend to release the aerosol rather noisily and violently, and may need a relatively high inspiratory flow rate to activate the spring. Perhaps for these reasons they are not widely used.

MDIs place quite high demands on patients' skill, and good tuition is essential. Physicians must demonstrate to patients, preferably using a placebo MDI, how to use their inhalers and must recheck their technique from time to time. MDI training aids may be useful for patients with poor coordination.[30] The use of manufacturers' instruction leaflets alone is not adequate, and there is a need for better and more standardised leaflets giving fewer conflicting instructions on inhaler technique. It is vital also that patients know that a diminished response to their inhalers means either that the canister is empty, that the inhaler is being used wrongly, or that their asthma is deteriorating; and they should take appropriate action urgently.

## SPACER ATTACHMENTS TO MDIS

Since particle size and velocity decrease with distance, the provision of a "spacer" between the patient's lips and the MDI will lead to small, slowly moving, respirable particles. This principle has led to the development of various types of spacer device or holding chamber, which literally holds the aerosol before this is inhaled. A 10 cm long tube spacer (volume approximately 100 $cm^3$) and a 25 cm cone spacer shaped like the aerosol spray cloud and with a one way inhalation valve (volume about 750 $cm^3$) are available commercially (the Bricanyl spacer inhaler or Pulmicort inhaler and the Nebuhaler, Astra Pharmaceuticals). In practice these spacers have several beneficial effects: (1) Oropharyngeal deposition is reduced, thereby reducing the incidence of oropharyngeal candidiasis and dysphonia with corticosteroid aerosol therapy.[31] (2) Drug delivery to the lung is improved, depending on the spacer design. The increase in lung deposition is less than the reduction in oropharyngeal deposition since many particles are deposited on the walls of the spacer itself. (3) Most importantly, the MDI is easier for the patient to use. The spray may be released into the spacer and inhaled after a brief pause, so that the need to synchronise firing and inhaling is either greatly reduced or entirely removed. In fact, firing a bronchodilator spray into the 10 cm tube spacer and delaying inhalation for three seconds is as effective as a correctly used MDI without a spacer attachment.[32] Thus spacers are probably of most value for patients with poor inhaler technique—particularly those who cannot synchronise firing the MDI with inhaling—and who may fail to obtain an adequate lung dose otherwise.

There have been many clinical trials with spacer devices, some of which have shown a greater therapeutic effect,[33 34] (but others no greater[35 36]) than the MDI alone. The discrepancies between the results of these trials may be related to the MDI inhalation manoeuvre used. While spacers may improve drug delivery to the lungs and therapeutic effect in those patients who have a poor inhaler technique, they may confer little additional clinical benefit for those who have a good inhaler technique[37]; and while good technique is most important with an MDI used alone, it may be less so when the MDI is combined with a spacer, though the effect of technique is not

necessarily negligible. Large volume holding chambers may be comparable to nebulisers in the delivery of larger doses of beta agonist aerosol used in the treatment of severe acute asthma.[38] Such chambers have the advantages of portability, simplicity of use, and ease of cleaning. By comparison with the conventional MDI, however, they are still large and bulky.

## DRY POWDER INHALERS

Dry powder inhalers[39] are a convenient alternative delivery system to MDIs. The first dry powder inhaler was introduced for sodium cromoglycate (Spinhaler, Fisons Ltd) and more recently inhalers have become available for dry powder preparations of salbutamol and beclomethasone dipropionate (Rotahaler, Allen and Hanburys Ltd). With the original cromoglycate preparation inhaled from a spinhaler the MMAD of the drug particles placed in the capsules was 2·6 $\mu$m and the lactose carrier powder had 70% of its mass between 30 and 60 $\mu$m in diameter.[40] About 5% of the dose reaches the lungs, according to pharmacokinetic studies.[41] Recently the capsule has been reformulated and the lactose powder omitted.

Having pierced or fractured the gelatin capsule containing the drug, all the patient has to do is to inhale through the device to draw the powder out of the capsule. Dry powder inhalers are thus easier to use than MDIs but less convenient because of the need to load a capsule into the device before use. They are usually reserved for patients who cannot master the technique of inhaling from an MDI. The correct inhalation technique for dry powder inhalers is unclear, although rapid inhalation ($\geq$60 l min$^{-1}$) leads to more efficient emptying of the capsules and better dispersion of the powder in the inhaled air stream. At the same time, rapid inhalation is likely to increase impaction losses in the oropharynx. The efficacy of various inhalation techniques for dry powder aerosols needs to be tested.

## NEBULISERS

In common with other types of inhalation device, the air driven jet nebuliser must be used correctly to achieve optimal drug delivery. Correct use in this case, however, depends relatively little on the patient's inhalation technique (most patients inhale by tidal breathing) and rather more on the way in which the nebuliser is set up and operated. The most important factor governing nebuliser performance is the flow of compressed air used to generate the aerosol. Aerosol size is inversely proportional to the compressed gas flow rate and a flow rate of $\geq$ 6 l min$^{-1}$ is necessary with most types of jet nebuliser . This ensures that treatment times are acceptably short,[42] and that the bulk of the aerosol mass is contained within particles of not more than 5 $\mu$m aerodynamic diameter.[43] It is insufficiently appreciated that the domiciliary oxygen cylinders available in Britain generally have two flow rate settings only, 2 and 4 l min$^{-1}$, and that these flows are inadequate for most of the better known brands of nebuliser. A wide range of electrically driven air compressors is now available but it is important to select carefully from this range and to ensure that the compressor can generate a sufficiently rapid air flow rate. The nebuliser may be powered by a hand held squeeze bulb or even a foot pump. These driving systems are relatively simple and portable, they allow the user to be independent of cylinders, and they are undoubtedly useful if nothing else is available. In practice, however, it is difficult to control the compressed air flow rate adequately.

There are several facts about nebulisers which are insufficiently appreciated. As with the MDI, only about 10% of the dose from a nebuliser reaches the lungs, most of it being retained as large droplets on the internal walls of the nebuliser itself.[44] Although much larger doses are customarily placed in nebulisers than are given from MDIs, the dose response curves may be similar for both.[45] The output depends on the volume fill and gas flow rate. Many pharmaceutical data compendia sheets recommend a 2 ml volume fill, although a higher percentage of the drug solution is released as aerosol if this volume is diluted to 4 or 6 ml.[42] Thus the dose from 2 ml may be inadequate. A combination of 4 ml volume fill and 6 l min$^{-1}$ gas flow rate is recommended to ensure a high aerosol output, small particle size, and short treatment time. A recent hospital questionnaire[46] showed that patients may be treated with nebulisers operated at flow rates varying from 1 to 10 l min$^{-1}$ and a diluent volume fill ranging from 0·5 to 10 ml. With many of these combinations the dose would be predictably inadequate.

Nebulisers may be used with either a facemask or a mouthpiece, according to the patient's preference.[47] Aerosol wastage on the face and in the nasopharynx will be greater with the facemask. The use of intermittent positive pressure breathing (IPPB) is often advocated with nebulised bronchodilators on the grounds that this "forces" more aerosol into peripheral lung regions. In fact, this technique appears to have no definite advantages over the inhalation of aerosol by tidal breathing[48] or the delivery of comparable doses of bronchodilator from an MDI.[49]

Nebulisers may be either "disposable" (to be discarded after each use) or "sterilisable." Most so called disposable nebulisers have a lifespan of two to three months if used carefully, but like the "sterilisable" nebulisers they must be thoroughly cleaned to

avoid bacterial contamination. Some types of nebuliser are difficult to clean since they cannot be taken apart, and furthermore the cleaning procedure may ultimately impair their performance. The filters and air intake grill on the air compressor should also be cleaned regularly. *Aspergillus* species have been cultured from fluff accumulating at these locations.[50] Also *Pseudomonas aeruginosa* is known to colonise water traps. When inhaled both may have potentially lethal consequences.

Ultrasonic nebulisers, in which high frequency sound waves are passed through liquid in a reservoir to create an aerosol, are widely used abroad but less so in Britain. Particle size and output may vary widely and have not been categorised satisfactorily. Also most require a mains electricity supply. Recently a portable, battery powered nebuliser based on a small, vertical rotating disc has been developed.[51] It has a lower aerosol output rate, however, than most jet nebulisers.

In recent years nebulisers have become popular for use both in hospital and in the home, particularly in the treatment of severe asthma. It is thought that a larger dose of bronchodilator might be delivered to the lungs more readily than with an MDI. Certainly this means of administration is tolerated well in adults and distressed children. Whether it fulfils all expectations remains debatable and there may be a partial placebo effect. Nevertheless, the nebuliser is a versatile device by which an increasingly wide range of drugs may be administered for topical and systemic treatment. There are some exciting prospects, which the second part of this review will discuss further.

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## References

[1] Ziment I. *Respiratory pharmacology and therapeutics.* Philadelphia: WB Saunders, 1978:1–7.
[2] Stuart BO. Deposition of inhaled aerosols. *Arch Intern Med* 1973;**131**:60–73.
[3] Swift DL. Generation and respiratory deposition of therapeutic aerosols. *Am Rev Respir Dis* 1980; **122**:71–7.
[4] Pavia D, Thomson ML, Clarke SW, Shannon HS. Effect of lung function and mode of inhalation on penetration of aerosol into the human lung. *Thorax* 1977; **32**:194–7.
[5] Palmes ED. Measurement of pulmonary air spaces using aerosols. *Arch Intern Med* 1973;**131**:76–9.
[6] Mercer TT, Goddard RF, Flores RL. Output characteristics of several commercial nebulisers. *Ann Allergy* 1965;**23**:214–20.
[7] Swithenbank J, Beer JM, Taylor DS, Abbott D, McCreath GC. A laser diagnostic technique for the measurement of droplet and particle size distribution. *Progress in Astronautics and Aeronautics* 1976; **53**:421–47.
[8] Lippmann M, Albert RE. The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. *Am Ind Hyg Assoc J* 1969;**30**:257–75.
[9] Foord N, Black A, Walsh M. Regional deposition of 2·5–7·5 $\mu$m diameter particles in healthy male non-smokers. *J Aerosol Sci* 1978;**9**:343–57.
[10] Morrow PE. An evaluation of the physical properties of monodisperse and heterodisperse aerosols used in the assessment of bronchial function. *Chest* 1981;**80**, suppl:809–13.
[11] Yu CP, Nicolaides P, Soong TT. Effect of random airway sizes on aerosol deposition. *Am Ind Hyg Assoc J* 1979;**40**:999–1005.
[12] Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airway obstruction. *J Appl Physiol* 1976;**40**:468–71.
[13] Goldberg IS, Lourenco RV. Deposition of aerosols in pulmonary disease. *Arch Intern Med* 1973;**131**:88–91.
[14] Newman SP, Killip M, Pavia D, Morén F, Clarke SW. Do particle size and airway obstruction affect the deposition of pressurised inhalation aerosols? *Thorax* 1983;**38**:233.
[15] Dolovich M, Ruffin R, Corr D, Newhouse MT. Clinical evaluation of a simple demand-inhalation MDI aerosol delivery device. *Chest* 1983;**84**:36–41.
[16] Clarke SW, Newman SP. Differences between pressurized aerosol and stable dust particles. *Chest* 1981;**80**, suppl:907–8.
[17] Newman SP, Morén F, Pavia D, Sheahan NF, Clarke SW. Deposition of pressurised aerosols in the human respiratory tract. *Thorax* 1981;**36**:52–5.
[18] Epstein SW, Manning CPR, Ashley MJ, Corey PN. Survey of the clinical use of pressurised aerosol inhalers. *Can Med Assoc J* 1979;**120**:813–6.
[19] Crompton GK. Problems patients have using pressurised aerosol inhalers. *Eur J Respir Dis* 1982;**63**,suppl 119:101–4.
[20] Frew AJ, Macfarlane JTM. Are medical staff any better at using inhalers than patients? *Thorax* 1982;**37**:780.
[21] Kelling JS, Strohl KP, Smith RL, Altose MD. Physician knowledge in the use of canister nebulisers. *Chest* 1983;**83**:612–4.
[22] Newman SP, Pavia D, Garland N, Clarke SW. Effects of various inhalation modes on the deposition of radioactive pressurised aerosols. *Eur J Respir Dis* 1982; **63**, suppl 119:57–65.
[23] Newman SP, Pavia D, Clarke SW. How should a pressurised $\beta$-adrenergic bronchodilator be inhaled? *Eur J Respir Dis* 1981;**62**:3–20.
[24] Williams TJ. The importance of aerosol technique: does speed of inhalation matter? *Br J Dis Chest* 1982: **76**:223–8.
[25] Lawford P, McKenzie D. Pressurised aerosol technique: influence of breath-holding time and relationship of inhaler to mouth. *Br J Dis Chest* 1982;**76**:229–33.
[26] Heimer D, Shim C, Williams MH. The effects of sequential inhalations of metaproterenol aerosol in asthma. *J Allergy Clin Immunol* 1980;**66**:75–7.
[27] Lawford P, McKenzie D. Pressurised aerosol inhaler technique: How important are inhalation from

residual volume, inspiratory flow rate and the time interval between puffs? *Br J Dis Chest* 1983;**77**:276–81.

[28] Muers M, Dawkins K. Effect of a timed interval between inhalation of beta agonist and corticosteroid aerosols on the control of chronic asthma. *Thorax* 1983;**38**:378–82.

[29] Connolly CK. Methods of using pressurised aerosols. *Br Med J* 1975;iii:21.

[30] Woolcock A. A training aid for pressurised inhalers. *Br J Dis Chest* 1980;**74**:395–7.

[31] Toogood JH, Jennings B, Baskerville J, Johansson SA. Clinical use of spacer systems for corticosteroid inhalation therapy: a preliminary analysis. *Eur J Respir Dis* 1982;**63**,suppl 122:100–7.

[32] Bloomfield P, Crompton GK, Winsey NJP. A tube spacer to improve inhalation of drugs from pressurised aerosols. *Br Med J* 1979;ii:1479.

[33] Lindgren SB, Formgren H, Morén F. Improved aerosol therapy of asthma: effect of actuator tube size on drug availability. *Eur J Respir Dis* 1980;**61**:56–61.

[34] Ellul-Micallef R, Morén F, Wetterlin K, Hidinger KC. Use of a special inhaler attachment in asthmatic children. *Thorax* 1980;**35**:620–3.

[35] Gomm SA, Keaney NP, Winsey NJP, Stretton TB. Effect of an extension tube on the bronchodilator efficacy of terbutaline delivery from a metered dose inhaler. *Thorax* 1980;**35**:552–6.

[36] Poppius H. Inhalation of terbutaline spray through an extended mouthpiece: effect on central and peripheral airways. *Respiration* 1980;**40**:278–83.

[37] Lindgren SB, Larsson S. Inhalation of terbutaline sulphate through a conventional actuator or a pear shaped tube: effects and side effects. *Eur J Respir Dis* 1982;**63**:504–9.

[38] Morgan MDL, Singh BV, Frame MF, Williams SJ. Terbutaline aerosol given through a pear spacer in acute severe asthma. *Br Med J* 1982;**285**:849–50.

[39] Crompton GK. Clinical use of dry powder systems. *Eur J Respir Dis* 1982;**63**,suppl 122:96–8.

[40] Bell JH, Hartley PS, Cox JSG. Dry powder aerosols I: A new powder inhalation device. *J Pharm Sci* 1971;**60**:1559–65.

[41] Walker SR, Evans ME, Richards AJ, Paterson JW. The fate of ($^{14}$C) sodium cromoglycate in man. *J Pharm Pharmacol* 1972;**24**:525–31.

[42] Clay MM, Pavia D, Newman SP, Lennard-Jones T, Clarke SW. Assessment of jet nebulisers for lung aerosol therapy. *Lancet* 1983;ii:592–4.

[43] Clay MM, Pavia D, Newman SP, Clarke SW. Factors influencing the size distribution of aerosols from jet nebulisers. *Thorax* 1983;**38**:754–8.

[44] Lewis RA, Fleming JS, Balachandran W, Tattersfield A. Particle size distribution and deposition from a jet nebuliser: influence of humidity and temperature. *Clin Sci* 1981;**62**:5P (abstract).

[45] Cushley MJ, Lewis RA, Tattersfield AE. Comparison of three techniques of inhalation on the airway response to terbutaline. *Thorax* 1983;**38**:908–13.

[46] Stainforth JN, Lewis RA, Tattersfield AE. Dosage and delivery of nebulised beta agonists in hospital. *Thorax* 1983;**38**:750–3.

[47] Stevenson RD, Wilson RSE. Facemask or mouthpiece for delivery of nebulised bronchodilator aerosols. *Br J Dis Chest* 1981;**75**:88–90.

[48] Fergusson RJ, Carmichael J, Rafferty P, Willey RF, Crompton GK, Grant IWB. Nebulised salbutamol in life threatening asthma: Is IPPB necessary? *Br J Dis Chest* 1983;**77**:255–61.

[49] Anderson PB, Goude A, Peake MD. Comparison of salbutamol given by intermittent positive-pressure breathing and pressure packed aerosol in chronic asthma. *Thorax* 1982;**37**:612–6.

[50] George RH, Gillet AP. Allergic bronchopulmonary aspergillosis. *Arch Dis Childhood* 1980;**55**:910.

[51] Malem H, Ward M, Henry D, Smith WHR, Gonda I. Early experience with a vertical spinning disc-nebuliser. *Lancet* 1981;ii:664–6.