LUNG MUCUS PRODUCTION AND MUCOCILIARY CLEARANCE: METHODS OF ASSESSMENT

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The primary defence mechanism of the tracheo-bronchial tree against all types of inhaled particles is the mucociliary escalator. This is composed of ciliated epithelium extending from the larynx to the terminal bronchioles (16th division of Weibel, 1963), on which lies a layer of mucus, the mucus blanket. As well as ciliated columnar cells, the tracheobronchial epithelium contains goblet cells which secrete mucus, the ratio between the two being 5 to 1 with a relative decrease in the number of goblet cells from the trachea to the lung periphery. Each ciliated cell has on its surface about 200 cilia of average length 6 μm and diameter 0.2 μm . Epithelial serous and Clara cells are also secretory cells, the latter being more numerous in the bronchioles and on occasion capable of transition to goblet cells on irritation. The submucosal glands are simple tubulo-alveolar structures present in the cartilage containing trachea and bronchial tree but not in bronchioles. Each gland contains both mucus and serous cells as well as myoepithelial cells which may serve to extrude secretions. In healthy adult humans the volume of glands down to the fifth generation bronchi has been calculated to be about 4 ml, in contrast to the goblet cell volume of 0.1 ml, or one fortieth of that amount (Reid, 1959). The submucus glands appear to be under cholinergic control, while goblet cells secrete on direct irritation (Brody, Waldhausen & Kuhl, 1971).

Tracheobronchial secretions are principally water (about 96%) and mucus (about 4%) formed by hydration of the extruded granules from the secretory cells. The secretions form a layer over the ciliary epithelium (Lucas & Douglas, 1934) which consists of a fluid periciliary sol which enables the cilia to beat freely and propel the uppermost gel layer up the airway (Figure 1). The original idea of a continuous mucus blanket 5–10 μ thick has been largely superseded by the concept of a periciliary sol on which flow discrete islands of gel (Iravani & Van As, 1972) like lilies on water. This makes theoretical calculations of secretion volume difficult.

The secretions contain sodium, chloride, potassium and calcium ions, while glycoproteins give the mucus its characteristic slimy texture. The glycoproteins have a protein core with multiple oligosaccharide side chains cross-linked by disulphide and hydrogen bonds. When viewed by the electron microscope, they

appear as a dense network of fibrous strands (Bürki, 1965). Hydrolysis of the side chains gives N-acetyl glucosamine, N-acetyl galactosamine, galactose, fucose and sialic acid. Other macromolecules synthesized locally include lysozyme, lactoferrin and immunoglobulins, chiefly IgA in normal subjects and IgE and IgG in asthmatics. Plasma proteins normally present in small amounts may leak into the airway secretions when there is inflammation of the surface epithelium. Other substances such as 5-hydroxytryptamine and histamine have been found and may be related to asthma.

The total volumes of secretions cleared per day in man is not clearly known owing to the difficulties in collection. Estimates range from 10 ml, measured in accident victims with tracheostomies (Toremalm, 1960), to 100 ml, where animal figures have been extrapolated to man (Policard & Galy, 1945). Patients with chronic bronchitis, however, may produce 30–100 ml/day in remission and 200–300 ml/day during exacerbations.

The flow rate of mucus in the human trachea varies from 5–20 mm min^{-1} (Yeates, Aspin, Levison, Jones & Bryan, 1975; Wood, Wanner, Hirsch & Farrell, 1975) with progressively slower rates towards the lung periphery (Serafini, Wanner & Michaelson, 1976). The fact that there is no significant build-up of secretions in the proximal airways during clearance has led to the supposition that reabsorption of secretions takes place, and this is supported by the fact that secretions in the peripheral airways are believed to be more watery than those in the central airways (Asmundsson & Kilburn, 1970). Clearance from the ciliated airways which extend to the terminal bronchioles by mucociliary action is complete within a matter of hours and certainly within one day (Camner & Philipson, 1978).

Physical properties of tracheobronchial mucus

Mucus has the physical properties of both a solid and a liquid; with slight stress it will deform and then reform when the stress is removed like an elastic solid but with greater applied stress it flows like a viscous liquid. It is non-Newtonian and probably thixotropic, so that, like paint, its apparent viscosity becomes less as the applied stress increases, causing it to flow more

Figure 1 Schematic diagram of the tracheobronchial mucosa and mucociliary escalator.

readily. *In vivo* viscosity and elasticity are difficult to measure in man and may well vary during such events as coughing, where airways narrow and high linear airflows lead to large shearing forces applied to the secretions. There is reason to believe that both properties are important with respect to normal mucus flow and hence optimal tracheobronchial clearance (Barnett & Miller, 1966), although elasticity may exert a dominant effect (Dulfano & Adler, 1975).

Purulent sputum is more viscous and has less elastic recoil than mucoid sputum and is thus cleared poorly. Likewise, severe asthmatics have visco-elastic plugs of mucus which are difficult to clear and expectorate. Recent work suggests that the surface properties, such as stickiness (Medici, Chodosh, Ishikawa & Eslein, 1978) and 'peelability' of mucus from the cilia (Silberberg, 1978), should also be taken into consideration.

Factors affecting the production of mucus

Inspired air is normally heated to body temperature and saturated with water vapour by the time it reaches the trachea. When cold dry air is breathed rapidly through the mouth or a tracheostomy, it stimulates secretion from the goblet cells, possibly as a protective mechanism. Other irritants also provoke the secretion of mucus, including ammonia, mustard, oil, sulphur dioxide and blood. They probably act partly by nervous pathways (possibly via cough receptors) and partly directly (possibly via pharmacological mediators).

Inflammation of the airways by viruses, bacteria or allergy increases mucus secretion but, again the precise mechanism is unknown.

Chronic exposure to cigarette smoke leads to increase in size of submucosal glands as well as the number of goblet cells, particularly in the bronchioles where few are normally found. These are the changes seen in subjects with chronic bronchitis, in whom smoking, infection and air pollution are important causative factors. Much of the work with drugs and respiratory mucus production has been done in animals *in vitro* and is not necessarily applicable to man. However, in human bronchial strips acetylcholine increases mucus secretion from both mucus and serous cells by increase in the pumping of chloride ions plus water by osmosis into the airway lumen (Nadel, Davis & Phipps, 1979). Atropine blocks the effect of cholinergic drugs in humans and may lessen tracheobronchial secretion from mucus glands, although the effect is small and the danger of mucus plugging by atropine in asthmatics has probably been overemphasized. A synthetic anticholinergic drug, ipratropium bromide, neither slows tracheobronchial clearance (Ruffin, Wolff, Dolovich, Rossman, Fitzgerald & Newhouse, 1978) nor increases mucus viscosity.

The effect of sympathomimetic drugs is uncertain. In animals adrenaline and related drugs may produce a small increase in respiratory secretion though not *in vitro* in man.

Pharmacological mediators have a variable effect on mucus secretions. Histamine increases sputum output in man as does prostaglandin ($\text{Pg F}_{2\alpha}$), though this is very irritant and may have a reflex action. Other mediators such as SRS-A and 5HT have not yet been tested.

The anatomy, physiology, pharmacology and pathology of tracheobronchial mucus secretion has

been reviewed in detail by Richardson & Phipps (1978).

Collection of tracheobronchial secretions

In man these secretions are difficult to collect since they are normally swallowed and when expectorated (i.e., coughed up) they are contaminated with saliva. This presents a major obstacle to the precise measurement of volume and rheological and physico-chemical studies. Toremalm (1960) collected secretions from the tracheostomy tubes of patients while Denton (1960) aspirated secretions through a bronchoscope. With the advent of fiberoptic bronchoscopy under local anaesthesia, lung lavage has become commonplace for collecting secretions and cells for cytology and culture (Haslam, Turton, Heard, Lukoszek, Collins, Salsbury & Turner-Warwick, 1980). However, it is less useful when collecting tracheobronchial secretions for rheological measurement, since the fact of being invasive and requiring drugs (e.g., lignocaine) which affect mucus secretion modify the very properties to be measured.

Measurements of tracheobronchial secretions

This topic lies somewhat outside the scope of the paper, and readers are referred to the reviews of Litt (1973), Richardson & Phipps (1978), and Nadel *et al.* (1979) for further details & references.

Mucociliary clearance

The cilia beat at a rate of 700–1000 beats min^{-1} with a whip-like action in coordinated metachronal waves travelling in the opposite direction to the flow of mucus, which is cephalad (Sleigh & Aiello, 1972). The power of the cilia is such that they can sweep against gravity and can carry weights up to 10 g cm^{-2} without dysfunction (Maxwell, 1905). Their energy source appears to be ATP distributed along the cilia, with one molecule per 700 Å (Kilburn, 1967). The cilia beat in the watery (sol) layer, while the hooks on their tips propel the viscid gel layer. Dysfunction of mucociliary transport may occur when the numbers of cilia are reduced, when the frequency of ciliary beat falls or becomes incoordinate or when the volume and rheological properties of the sol and gel layers change (Wanner, 1979). These factors may act singly or in combination.

Coughing occasionally augments mucociliary clearance in normal subjects, becoming more obvious when secretions are increased in respiratory infections. After a brief pause at full inspiration, an explosive acceleration to peak expiratory flows coupled with expulsive airway narrowing ensures a high linear flow capable of shearing secretions from the airway walls, and causing expectoration (Leith,

1968). Since the cross sectional area of the airways diminishes progressively from the terminal bronchi to the trachea, linear velocities will be much higher in central airways from the trachea to 7–8th airway generation. Linear velocities which should exceed 2.5 m s^{-1} to shear secretions are achieved with peak flows of 5–10 l s^{-1} . Where there is serious airflow obstruction in chronic bronchitics or asthmatics, peak flows may be insufficient to reach satisfactory linear velocities despite extreme expiratory airway narrowing. Thus cough may be inefficient and tiresome in these patients. Velocities achieved in efficient coughing may amount to 160–240 m s^{-1} (50–75% the speed of sound) (Clarke, Jones & Oliver, 1970; Jones & Clarke, 1970). Where ciliated cells cease in the terminal bronchioles, alveolar clearance takes over (Green, 1973; Morrow, 1973). Movement of particles in this region is believed to be effected by the alveolar macrophage which engulfs the particle and migrates either towards the bronchial lumen or into subpleural, paraseptal, perivascular, peribronchial locations or into bronchiolar lymphatics whence to the lymphoid nodules. In contrast to mucociliary clearance, the clearance of particles by this mechanism is slow, taking several months at least.

Measurement of mucociliary clearance in man

This paper is concerned with techniques applicable to man *in vivo*, of which there are three.

Radioaerosol technique

This involves the inhalation of an aerosol firmly tagged with a gamma-emitting radionuclide which can be monitored by external chest counters. The initial deposition can be ascertained, as can the subsequent clearance, resulting in a fall and changing pattern of radioactivity, provided allowance is made for the physical decay of the radionuclide. After correction for decay, a typical curve is seen (Figure 2). It is divided conventionally into two phases, an early fast phase and a later slow phase. The fast phase represents mucociliary clearance of particles, augmented by cough on occasion. It takes less than 6 h for 90% to be cleared in healthy subjects. The slow phase represents alveolar clearance and is the radioactivity remaining at 24 hours and longer (Camner & Philipson, 1978). This is assumed to be due to deposition on non-ciliated terminal airway units. If the estimated alveolar clearance is subtracted from fast-phase mucociliary clearance, this gives tracheobronchial clearance. Alveolar clearance is an assumption, since there is no way of measuring this directly in man. As such it has been challenged and the suggestion made that this could be slow phase mucociliary clearance in peripheral airways,

Figure 2 (a) Diagrammatic curve showing fast and slow phases of lung clearance following inhalation of radioaerosol. (b) Fast phase tracheobronchial clearance obtained by subtracting the 24 h count (alveolar deposition) from the initial portion of curve (a).

particularly if they were diseased. Nevertheless, to all intents and purposes, it is a useful working concept.

The rate of clearance of the particles is closely related to their initial deposition, which itself is dependent on the physical properties of the aerosol, the mode of inhalation (i.e., flow rate, breath volume) and the patency of the airways (i.e., whether there is airways obstruction).

The significant properties of aerosols are particle size, density, hygroscopicity and electrical charge. The bigger the particle size, the more likely it is to deposit by impaction near the mouth (Lippmann & Albert, 1969; Pavia & Thomson, 1976). Greater density increases the aerodynamic diameter ($d_a = d\rho^{1/2}$), causing the particle to behave aerodynamically like a bigger unit density particle (Morrow, 1974). A hygroscopic particle will absorb water and grow during inspiration. The effect of electrical charge is unknown.

The mode of inhalation affects aerosol deposition. A large volume breath ensures that more particles will deposit in the peripheral airways (Booker, Chamberlain, Rundo, Muir & Thomson, 1967) whilst a high flow breath causes more central deposition by turbulent impaction (Goldberg & Lourenço, 1973;

Pavia, Thomson, Clarke & Shannon, 1977). Breath holding allows particles to settle out at the furthest point of entry (Newman, Pavia, Bateman & Clarke, 1980 unpublished observations). Airflow obstruction leads to more central deposition due to impaction (Thomson & Short, 1969; Dolovich, Sanchis, Rossman & Newhouse, 1976).

The rate of clearance of particles deposited on the ciliated airways is proportional to the transit pathway, peripheral particles taking proportionally longer than central particles (Thomson & Pavia, 1974). This must be taken into account in any analysis of clearance by monitoring the initial deposition pattern with a rectilinear gamma scanner (Dawson, Douglas, Pavia, Reeves, Short & Thomson, 1971) or a gamma camera (Bateman, Newman, Daunt, Pavia & Clarke, 1979). Alternatively a 24 h count will show the aerosol remaining in terminal non-ciliated airways (Albert, Lippmann, Peterson, Berger, Sanborn & Bohning, 1973).

The type of monitor depends on the dose of radioactivity used. For high lung burdens ($> 100 \mu\text{Ci}$ of $^{99}\text{Tc}^m$) the gamma camera provides information on the distribution of aerosol and allows regional clearance to be assessed (Sanchis, Dolovich, Chalmers & Newhouse, 1972). For medium doses of lung activity ($< 30 \mu\text{Ci}$ of $^{99}\text{Tc}^m$) a suitably collimated single central anterior chest counter will suffice to measure clearance (Toigo, Imarisio, Murmall & Lepper, 1963). It is better however to use twin axially opposed detectors placed antero-posteriorly (Thomson, Pavia, Gregg & Stark, 1974) or laterally (Philipson, 1977), or a series of detectors placed round the chest wall (Albert, Lippmann & Briscoe, 1969). For low doses of radioactivity ($< 1 \mu\text{Ci}$ of $^{99}\text{Tc}^m$) a whole body scintillation counter can be used.

The repeatability of the clearance curves for groups of subjects is good (Figure 3-propranolol and control), with a standard error of $\pm 4\%$, though there appears to be more variation in the individual subject. The significance of the difference between any two curves is tested by the paired *t*-test. With small numbers of patients where the data are not normally distributed, the Wilcoxon test is used.

2. Local mucus velocity techniques

Cinebronchofiberscopic technique Sackner, Rosen & Wanner (1973) devised the cinebronchofiberscopic and roentgenographic technique to measure the rate of movement of small (0.13 mg) teflon discs blown into the trachea. Tracheal mucus velocity (TMV) is derived by measuring the time taken for the discs (about 10–20 in number) to move a given distance.

An alternative to this method involves mixing the teflon discs with a radio-opaque marker, bismuth

Figure 3 Effect of (a) hyoscine ($n = 10$), (b) hypertonic saline ($n = 11$) propranolol ($n = 9$), (c) and (d) chest physiotherapy at arrow ($n = 8$) on lung clearance curves. — hyoscine, propranolol or hypertonic saline respectively, control.

trioxide, and measuring the tracheal mucus velocity from the motion of these insufflated particles visualized by fluoroscopic image intensifier, television monitor and video tape (Goodman, Yergin, Landa, Golinvaux & Sackner, 1978).

Radio-isotopic bronchoscopic technique Chopra, Taplin, Elam, Carson & Golda (1979) described this technique whereby a graduated fiberoptic bronchoscope is used to determine the length of trachea from carina to larynx by marking these sites with a radioactive tracer for recording on polaroid film from a gamma camera. A small (40 μ l) suspension containing about 50,000 albumin particles (5–7 μ m diameter) tagged with $^{99}\text{Tc}^{\text{m}}$ is deposited near the carina by catheter inserted through a fiberoptic bronchoscope. In this case, movement of the particles is measured by serial (1 min) polaroid pictures from the gamma camera, for the half an hour approximately that the particles take to traverse the trachea.

Radioaerosol boli technique Yeates *et al.* (1975) were able to deposit a bolus of aqueous aerosol containing $^{99}\text{Tc}^{\text{m}}$ albumin microspheres (0.5 μ m median diameter) centrally by inhaling near total lung

capacity at a high flow rate. Thereafter movement of the bolus was recorded by gamma camera.

3. Tantalum bronchographic technique

Tantalum powder insufflated through a catheter placed at the carina will allow X-ray visualization of representative airways from the trachea to terminal bronchioles (Gamsu, Weintraub & Nadel, 1973). Serial chest X-rays thereafter (at 0, 4, 8, 16, 24 and 48 h) will give an indication of the tantalum remaining (based on scoring by an observer). This technique is, therefore, capable of measuring whole lung mucociliary clearance as well as local mucus velocity. However, technical problems have led to it being little used.

The advantages and disadvantages of these techniques for measuring lung mucociliary clearance in man are listed in Table 1.

Factors affecting mucociliary clearance

Physiological

While mucociliary clearance appears to slow with age (Goodman, *et al.*, 1978), there is no difference between the sexes (Pavia, Short & Thomson, 1970; Yeates, *et al.*, 1975), nor does posture have any effect (Wong, Keens, Wannamaker, Douglas, Crozier, Levison & Aspin, 1977). During sleep clearance appears to slow considerably in healthy subjects (Bateman, Pavia & Clarke, 1978), a finding which may have important implications in patients with chronic bronchitis or asthma, in whom early morning cough, sputum and wheeze may be a predominant feature. There is no circadian rhythmicity (Bateman, Clarke, Pavia & Sheahan, 1978). Finally, exercise increases clearance in healthy subjects, as does eucapnic hyperventilation to a lesser degree (Wolff, Dolovich, Obminski & Newhouse, 1977).

Environmental pollutants

The effect of smoking on clearance is uncertain. In some studies on long term smokers, clearance has been slow (Lourenço, Klimek & Borowski, 1971), while in others it was normal (Thomson & Pavia, 1975). In acute cigarette inhalation studies both slowing of mucociliary clearance (Pavia, Thomson & Pocock, 1971) and speeding (Camner, Philipson & Arvidsson, 1971) have been reported. Neither SO_2 , sulphuric acid mist nor aerosol propellants have any definite effect on clearance, though hair spray has been noted to reduce tracheal mucus velocity (Friedman, Dougherty, Nelson, White, Sackner & Wanner, 1977).

Diseases

In chronic bronchitics, clearance is either normal (Thomson & Short, 1969) or decreased (Bertrand & Puchelle, 1977) but may be augmented by coughing (Camner, Mossberg, Philipson & Strandberg, 1979).

In asthmatics, clearance appears to be reduced even when the asthma is mild (Bateman, Pavia, Sheahan & Clarke, 1979a). There is some evidence that clearance may slow progressively as the asthma deteriorates culminating in the mucus plugging which is severe and widespread in asthmatics who die in an attack

Table 1 Advantages and disadvantages of techniques used for measuring lung mucociliary clearance in man

<i>Technique</i>	<i>Advantages</i>	<i>Disadvantages</i>
Radioaerosol	<ol style="list-style-type: none"> 1. Non-invasive 2. Measures mucociliary clearance from all the ciliated airways 3. Amount of tracer used is of the order of a few μg 4. Low radiation dose to the lungs 	<ol style="list-style-type: none"> 1. Clearance related to initial distribution of radioaerosol within the lungs 2. Long observation periods (up to 24 h) 3. Artefacts in clearance due to coughing (unless steps are taken to correct for it)
Cinebronchofiberscopic	<ol style="list-style-type: none"> 1. Short observation period (2–30 min) 	<ol style="list-style-type: none"> 1. Invasive
Roentgenographic	<ol style="list-style-type: none"> 2. Artefacts due to coughing are minimized 	<ol style="list-style-type: none"> 2. Limited to large airways and often sampling from a small portion of airway
Radioisotopic-bronchoscopic	<ol style="list-style-type: none"> 3. Repeat measurements within a short period of time 4. Yields measurement of mucus velocity in anatomically well defined airways (usually the trachea) 	
Insufflated radio-opaque powder (Tantalum)	<ol style="list-style-type: none"> 1. Sampling from all the ciliated airways 2. Measurements in anatomically well defined airways 	<ol style="list-style-type: none"> 1. Invasive 2. Semi-quantitative 3. Long observation period 4. Artefacts due to coughing 5. Amount of powder used is several grams 6. High radiation dose to the lungs

Table 2 Tracheal mucus velocities (TMV) for healthy subjects

<i>Technique</i>	<i>Number of subjects</i>	<i>Mean $\pm$ s.d. TMV (mm min⁻¹)</i>	<i>Reference</i>
Cinebronchofiberscopy	20	20.1 $\pm$ 6.3	Wood <i>et al.</i> (1975)
Radioisotopic-bronchoscopic	6	15.5 $\pm$ 0.7	Chopra <i>et al.</i> (1979)
Roentgenographic	10*	10.1 $\pm$ 3.5	Goodman <i>et al.</i> (1978)
	7**	5.8 $\pm$ 2.6	
Radioaerosol boli	42	4.7†	Yeates <i>et al.</i> (1975)

*Young subjects

**Older subjects

†s.d. not given

(Hilding, 1943). Clearance is reduced in bronchiectasis (Loureço, Loddenkemper & Carton, 1972), influenza A infection (Camner, Jarstrand & Philipson, 1973) and mycoplasma pneumonia (Jarstrand, Camner & Philipson, 1974). In cystic fibrosis, lung mucociliary clearance appeared unimpaired, when measured by radioaerosol though central deposition occurred due to the accompanying lung disease. There are no studies on healthy children for comparison (Sanchis, Dolovich, Rossman, Wilson & Newhouse, 1973). When tracheal mucus velocity was measured with a marker technique in patients with cystic fibrosis it was 25% of normal (Wood *et al.*, 1975).

Male infertility has been linked with defective clearance (Camner, Mossberg & Afzelius, 1975) in Kartagener's syndrome (situs inversus with sinusitis and bronchiectasis), as well as in the 'immotile cilia syndrome', in which there is no situs inversus (Elliason, Mossberg, Camner & Afzelius, 1977). In both, the cilia and sperm tails which are structurally similar, are abnormal. Young's syndrome is similar except that the cilia appear structurally normal but sperm transport in the epididymis is completely absent (Hendry, Knight, Whitfield, Stansfield, Pryse-Davies, Ryder, Pavia, Bateman & Clarke, 1978). Other types of ciliary defect have been described suggesting a spectrum of related disorders which is currently exciting much interest.

Drugs

Hitherto, mucolytics and expectorants have been evaluated subjectively by measuring any effect on pulmonary function and changes in the chemistry and visco-elasticity of sputum. To these can be added the recent objective *in vivo* techniques, which show improved clearance after bromhexine in bronchitics (Thomson, Pavia, Gregg & Stark, 1974) but not after S-carboxy-methylcysteine for instance (Thomson, Pavia, Jones & McQuiston, 1975). Water aerosol gives a small increase, whereas normal saline, and particularly hypertonic (7.1%) saline, produces a marked improvement (Pavia, Thomson & Clarke, 1978). β -adrenoceptor agonists such as terbutaline may increase clearance when given parenterally (Mossberg, Strandberg, Philipson & Camner, 1976), but this effect is less sure when given by inhaler in patients with reversible airflow obstruction (Bateman, Pavia, Sheahan & Clarke, 1979b). β -adrenoceptor blockers, however, do not appear to impair clearance (Bateman, Lennard-Jones, Pavia & Clarke, 1980).

Anticholinergic drugs such as hyoscine (Pavia & Thomson, 1971 and atropine (Foster, Bergofsky, Bohning, Lippmann & Albert, 1970) reduce clearance while a cholinergic drug, bethanecol, increased clearance (Camner, Strandberg & Philipson, 1974). The

synthetic anticholinergic drug ipratropium bromide had no adverse effect on clearance (Pavia, Bateman, Sheahan & Clarke, 1979).

Studies have also measured the effect of steroids (Bateman, Agnew, Sheahan, Pavia & Clarke, 1980 unpublished observations), sodium cromoglycate (Mezey, Cohn, Fernandez, Januszkiewicz & Wanner, 1978), oxygen therapy (Sackner, Landa, Hirsch & Zapata, 1975) and general anaesthetics on clearance (Lichtiger, Landa & Hirsch, 1975; Gamsu, Singer, Vincent, Berry & Nadel, 1976). Chest physiotherapy has also been investigated and found to be very effective in clearing secretions (Bateman *et al.*, 1979). Lung clearance curves after hyoscine, propranolol, hypertonic saline and chest physiotherapy are shown in Figure 3.

Comparison of methods

The foremost method of measuring whole lung mucociliary clearance is the radioaerosol technique. The clearance rate is closely related to the initial distribution of radioaerosol within the lungs, and the distribution depends on aerodynamic particle size and the inhalation procedure. Since few centres use an identical technique, comparison of clearance curves between centres is imprecise. When heterodisperse are used instead of monodisperse (uniform size) particles, the larger particles carrying a large amount of radioactivity are deposited centrally, and thus influence the clearance curve. Some workers using monodisperse particles aim for central deposition with a short observation period (1–3 h) subsequently. However, there is no way of ensuring that deposition is identical between runs or over how many airway generations clearance is sampled. Other workers aim to label the whole of the tracheobronchial tree by obtaining an average tracheobronchial clearance curve. This requires prolonged observation with frequent readings for 6 h and a final reading at 24 h. With this method, an initial scan with a gamma camera or scanner of the topographical distribution of radioaerosol within the lung gives an estimate of the transit path which the tracer has to traverse. The 24 h measurement indicates the proportion of the radioaerosol deposited on non-ciliated airways.

The bronchoscopic techniques are invasive but have some advantages. A short observation period (several minutes) permits serial measurements over a relatively short time and minimizes changes in clearance due to coughing, for instance. Furthermore, the tracer can be accurately sited and mucus velocity measured in a clearly defined area. However, the technique is restricted to the large airways and mainly the trachea. There is no guarantee that the tracheal rate is the same as elsewhere in the bronchial tree.

A list of measurements of tracheal mucus velocities is given in Table 2. The invasive techniques using the fiberoptic bronchoscope yield considerably higher values than those obtained by the non-invasive radioaerosol boli technique. Recent work has suggested that local radioactivity from the bolus may itself speed velocity (Ahmed, Januszkiewicz, Landa, Brown, Chapman, Kenny, Finn, Bondick & Sackner,

1979).

The radioaerosol technique has the advantage of being non-invasive and of providing a measure of clearance from all the ciliated airways. The radiation dose to the lungs is a fraction of that from a chest X-ray. However, it requires long observation periods (1–24 h), during which coughing may be a problem to be accounted for.

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