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GROWTH RATE MEASUREMENTS AND DEPOSITION MODELLING OF HYGROSCOPIC AEROSOLS IN HUMAN TRACHEOBRONCHIAL MODELS

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Abstract—A laboratory system has been developed in which the atmosphere and fluid dynamics of the upper tracheobronchial (TB) tree of the human are simulated. It is used to measure the hygroscopic growth rates of monodisperse NaCl and bronchodilator (Isuprel® hydrochloride with and without glycerine) aerosols. Dry particles are mixed with water vapour-laden air at the entrance to a growth chamber temperature controlled at 37°C with a relative humidity (RH) between 88 and 95%. Hygroscopic growth rates increased with degree of RH and magnitude of Reynolds number in the chamber. The growth data are incorporated into an aerosol deposition model to calculate the effect of hygroscopic growth upon the dose distribution of medicinal aerosols in the human TB network. The model uses some original deposition formulae to compute particle deposition efficiencies. Calculations show that the rate of water vapour absorption within TB airways is an important factor affecting the fate of particles used in aerosol therapy.

NOMENCLATURE

The nomenclature used in the development of theoretical formulae is as follows:

- λ = mean free path of gas molecules in air
- g = gravitational constant
- k = Boltzmann constant
- T = absolute temperature (K)
- l_i = length of an airway of Weibel generation i
- r_i = radius of an airway of Weibel generation i
- ν = kinematic viscosity of air
- η = absolute viscosity of air
- $\bar{u}_i$ = mean air velocity in an airway of Weibel generation i
- d = particle geometric diameter
- m = particle mass
- $C(d)$ = particle slip correction factor

$$= 1 + A \frac{2\lambda}{d}$$

$$\text{where } A = 1.257 + 0.4 \exp \left(-1.1 \frac{d}{2\lambda} \right)$$

ϕ_i = inclination of an airway of Weibel generation i with respect to the horizontal

Re_i = airflow Reynolds number

$$= \frac{2r_i \bar{u}_i}{\nu}$$

τ = particle relaxation time

$$= \frac{mC(d)}{3\pi\eta d}$$

v = particle Stokes terminal settling speed

$$= \tau g$$

D = particle diffusion coefficient

$$= \frac{kT\tau}{m}$$

INTRODUCTION

THE SUCCESS of aerosol therapy in the treatment of obstructive lung diseases may be related to the total dose delivered to the lung and its regional distribution (MORROW, 1974). The TASK GROUP ON LUNG DYNAMICS (1966) has shown that the efficiency with which inhaled particulate matter is deposited within the human respiratory tract is a function of the mass median aerodynamic diameter (*MMAD*) of the aerosol particle size distribution. The *MMAD* of several bronchodilator aerosols, including isoproterenol hydrochloride, produced by metered-dose devices have been determined by HILLER *et al.* (1978). Some of these aerosols are hygroscopic and may absorb water vapour, or evaporate, while travelling through humid respiratory passages. Consequently, the *MMAD* of such aerosols will vary with position in the human tracheobronchial (TB) tree and their deposition patterns may differ from those for non-hygroscopic aerosols of the same initial size.

We have measured the rates of growth of two commercially available hygroscopic bronchodilator aerosols, Isuprel® hydrochloride with and without glycerine, in an experimental system which simulates the gas dynamics and temperature and relative humidity environment of the human lung. The hygroscopic behaviour of NaCl was also studied, since many therapeutic aerosols are generated from saline solutions, and such particles may be considered as being NaCl tagged with a medicinal agent. Understanding the physical and chemical mechanisms controlling aerosol growth is a foundation for the development of new mathematical models for predicting the dose distribution of hygroscopic aerosols in the human respiratory tract. Similar considerations may aid in selecting additives to control the growth and deposition of inhaled therapeutic drugs.

Past attempts to calculate the deposition efficiency of hygroscopic particles in the human respiratory tract have either assumed a fixed aerodynamic particle diameter (D_{ae}) throughout the TB tree or used theoretically calculated particle growth rate curves (MILBURN *et al.*, 1957; TASK GROUP ON LUNG DYNAMICS, 1966; FERRON, 1977).

To predict more accurately the deposition of hygroscopic aerosols, we have developed a new analytical model. Theoretical deposition efficiency formulae are derived for both turbulent and laminar conditions, and hygroscopic particles are allowed to have a continually changing aerodynamic size throughout the TB tree. Experimental particle growth rate curves measured in a simulated TB environment are used to specify the latter particle sizes within airways. The model calculates the total dose and the regional distribution of inhaled particulate matter as a function of aerodynamic particle size and inspiratory flow rate. The deposition efficiency and site of deposition of hygroscopic medicinal aerosols are compared to non-hygroscopic aerosols of like inhaled *MMAD*. The effect of glycerine upon the deposition patterns of the Isuprel® hydrochloride bronchodilator aerosols is also calculated.

GROWTH RATE MEASUREMENTS OF HYGROSCOPIC AEROSOLS

Experimental apparatus and methods

Figure 1 is a schematic diagram of the laboratory system used to measure the growth rates of hygroscopic particles. A vibrating orifice instrument (Berglund-Liu Monodisperse Aerosol Generator, Thermosystems Model 3050, St Paul, Minnesota) is used to generate dry monodisperse aerosols. The aerosol flows at 1–3 l. min⁻¹ through copper tubing immersed in a temperature controlled (37°C) water bath and passes into a 5 cm i.d. copper growth tube. Clean compressed air is precisely metered, heated, humidified and temperature regulated so as to deliver between 50 and 100 l. min⁻¹ of water-saturated air at 37°C to mix with the monodisperse dry aerosol particles at the entrance to the growth chamber. This compressed air enters the top of the growth chamber through four ports located symmetrically about its perimeter. A Climet 208 optical particle counter samples the mixture at 7 l. min⁻¹ and the excess leaves the growth chamber through four exit ports. By maintaining steady plug flow in the growth chamber and Climet sampling tube, the time for aerosol particle growth may be determined from the specified aerosol and compressed air flow rates, and the known

FIG. 1. Schematic diagram of the experimental apparatus for measurement of the growth rates of hygroscopic aerosols.

distance between the point where dry monodisperse aerosol particles enter the growth chamber and the location at which the geometric diameters of the aerosol are measured by the optical particle counter. The growth time may be increased by adding sections to the growth chamber or by decreasing the compressed air flow rate. In the experiments, growth times ranged from 0.05 to 1.0 s. The relative humidity and temperature in the growth chamber are monitored by a micropsychrometer (two 0.08 mm dia. chromium constantan thermocouples, one wrapped with a water-saturated wick to give the wet bulb temperature) situated near the aerosol entrance, and by a dewpoint hygrometer (Model 880, EG & G, Waltham, Massachusetts) and dry bulb temperature probe located at one of the exhaust ports. Water condensation in the growth chamber and droplet evaporation in the Climet sampling tube is avoided by enclosing the units in a box within which the temperature was controlled at 37°C by the circulation of heated air.

Three different monodisperse aerosols were generated for use in our work: NaCl particles and particles from two different stock solution forms of the drug Isuprel® hydrochloride (Winthrop Laboratories, New York, New York). The commercially available forms of Isuprel® hydrochloride (a bronchodilator) are 1.0 and 0.5% Isuprel® hydrochloride. The former contains 1% (by weight) of the active bronchodilator agent isoproterenol hydrochloride and 0.183% of NaCl. The latter contains 0.5% isoproterenol hydrochloride and 0.37% of NaCl. They also contain a multitude of buffering and preserving agents. Their major difference in chemical composition is that the 0.5% Isuprel® hydrochloride solution contains 8% (by weight) of glycerine while the other has no glycerine. Glycerine is apparently added because it is a humectant and may, therefore, inhibit the rate of evaporation of aerosol droplets.

Conditions in the growth chamber are chosen to simulate both the atmosphere (temperature and relative humidity) in the upper TB tree and the fluid dynamics of the laryngeal jet. DERY *et al.* (1967) made relative humidity measurements in the trachea and large airways of anaesthetized human subjects. Values were found to range from 90 to 95%. Hence, such relative humidities were maintained in the growth chamber. Likewise, the temperature was kept at 37°C to simulate body temperature. Inhaled air enters the trachea through the larynx in the form of a jet. The influence of this laryngeal jet upon the deposition of non-hygroscopic particles has been experimentally quantitated by SCHLESINGER and LIPPMANN (1976). In our work, therefore, dry aerosol particles are injected into the growth chamber in an attempt to simulate the effect of the laryngeal jet upon mixing and hygroscopic growth.

These studies of the growth rates of initially dry bronchodilator aerosols are analogous to inhalations of metered-dose bronchodilator aerosols from hand-held devices. Most such drugs are packaged as a micronized powder together with fluorocarbon propellant and dispersing and surface active agents.

Hygroscopic growth rate curves

Figure 2 compares experimental growth data for sodium chloride and Isuprel® hydrochloride particles with the theory for sodium chloride growth at 25°C and various relative humidity conditions developed by CRIDER *et al.* (1956). The latter theory assumed that particles are completely and instantaneously surrounded by saturated air and then commence to absorb water vapour. In our experimental work, however, such ideal mixing does not occur because of the attempt to be physiologically

FIG. 2. Sodium chloride and Isuprel® hydrochloride growth rate data (34–38°C, Reynolds number = 2124–2328) compared with the theory of CRIDER *et al.* (1956) for sodium chloride at 25°C.

realistic. d_0 and d_t are, respectively the geometric particle diameters initially and after growth time t . The normalized growth time, $t/m_0^{2/3}$ (m_0 = initial dry particle mass) is calculated from d_0 and the dry particle densities of 2.165, 1.32 and 1.48 respectively for NaCl, 0.5% Isuprel® hydrochloride and 1% Isuprel® hydrochloride. The data show that NaCl and 1% Isuprel® hydrochloride (without glycerine) particles, grow at approximately the same rate in the 90–95% relative humidity range. However, the effect of glycerine in the 0.5% Isuprel® hydrochloride solution is to reduce the initial rate of growth. This suggests that glycerine can reduce the rate at which water vapour is condensed onto an airborne particle.

The experimentally measured growth rate data for sodium chloride fall below that predicted by the CRIDER *et al.* (1956) growth theory, presumably because dry aerosol particles are not mixed ideally with saturated air at the entrance to the growth tube. Consequently, the effective growth period in which the particle is surrounded by air at the specified relative humidity is sufficiently less to result in noticeable growth rate differences.

As the flow rate of humidified air increases through the growth chamber, the Reynolds number (or degree of turbulence) increases and more rapid mixing of the dry aerosol and wet air stream at the entrance to the growth tube may be expected. Figure 3 shows the dependence of 1.0% Isuprel® hydrochloride particle growth rates on the Reynolds number in the growth chamber. Particle growth rates increase monotonically with the Reynolds number. For $Re \geq 2200$, turbulent flow should be maintained along the growth tube. For $Re < 2200$, however, the turbulence generated by mixing in the humidified air should decrease in intensity along the growth chamber, just as the turbulent eddies generated by the larynx during normal inhalations are predicted to be attenuated (OWEN, 1969). For steady flow simulating resting conditions Re is about 1000 in the human trachea, so with moderate exercise and work Re should be in the 2000–3000 range.

FIG. 3. Dependence of the growth rate of 1% Isuprel® hydrochloride (without glycerine) particles on turbulent mixing. $d_0 = 1.79 \mu\text{m}$ at 45% RH. Growth measured at 34–35.5°C, 89–93% RH, and $Re = 1037 - 2604$.

HYGROSCOPIC AEROSOL DEPOSITION MODEL

Mathematical computation of hygroscopic aerosol deposition in the human TB tree requires (i) selection of a suitable respiratory tract geometry, (ii) description of TB gas dynamics including the influence of the laryngeal jet upon the onset of turbulence, (iii) selection of a system of formulae describing particle deposition efficiencies and (iv) data describing hygroscopic growth behaviour.

TB morphology

The human TB tree is a branching system of flexible airways which may be curved and of irregular cross-section. Various simplified descriptions, symmetric and asymmetric, exist which differ in airway dimension, orientation and mode of branching (FINDEISEN, 1935; WEIBEL, 1963; HORSFIELD *et al.*, 1971; YEH *et al.*, 1976). These descriptions consider TB airways to be rigid cylinders of circular cross-section. The simple Model A of Weibel which assumes a symmetric dichotomous branching pattern is the easiest to use in deposition calculations and has not been shown to be inferior to the more complex models. In this geometry, selected for use in our work, the conducting airways of the TB tree consist of 16 successive generations; the trachea is generation 0 and the final terminal bronchiole is generation 16. The number of airways in generation i is 2^i .

Aerodynamics within the TB tree

Airflow patterns in replica casts of the human upper TB tree have been studied at

tracheal flow rates from 5 to 80 l. min⁻¹ (WEST and HUGH-JONES, 1959). The onset of turbulence in the trachea was noted at 20 l. min⁻¹. Since the casts did not have a larynx, turbulence was attributed to the branching TB geometry and airway surface irregularities. The turbulent motion became dampened with progression through the branching network of the TB tree. For tracheal flow rates up to 40 l. min⁻¹, laminar motion existed in lobar and distal bronchi, and was turbulent in proximal airways. As the flow rate was increased to 80 l. min⁻¹ the turbulence persisted to the segmental bronchi. The transition between laminar and turbulent flow in casts of the trachea and main bronchi of humans with and without a larynx has also been investigated by DEKKER (1961). In the absence of a larynx, flow remained laminar in the trachea for steady flow rates up to 21 l. min⁻¹, but with a larynx turbulence occurred at 6 l. min⁻¹. SCHROTER and SUDLOW (1969) measured airflow patterns in both idealized models of bronchial bifurcations and replica casts of human lungs. Steady inspiratory flows appropriate to man at rest were studied. Flow patterns observed in bronchi were laminar but very asymmetric. Taking these experimental observations into account, laminar plug flow is assumed in our work for generations 0–3 when the inspiratory flow rate is less than 6 l. min⁻¹ and for generations 4–16 for all flow rates. When 6 l. min⁻¹ is surpassed, however, turbulent airflow is assumed in generations 0–3 (trachea, main, lobar and segmental bronchi).

Aerosol deposition probability formulae

Deposition of inhaled aerosols within conducting airways of the TB tree may be attributed primarily to the action of three mechanisms: inertial impaction, sedimentation and diffusion. The motion of the particles in the 1–10 μm D_{ae} size range is dominated by the inertial impaction and sedimentation mechanisms. The movement of smaller submicron particles is mostly due to diffusion. Particles larger than 10 μm in D_{ae} are mostly deposited proximal to the trachea in either the oral pharyngeal compartment (for mouth breathing) or the larynx.

Deposition by inertial impaction takes place at airway bifurcations, or carinae, when particles have sufficient mass and velocity so that their trajectories deviate from air streamlines which are curved because of the branching nature of the TB network. Beyond the carinae, deposition by sedimentation can occur when the gravitational acceleration has a component directed toward the wall of an airway. The deposition efficiency of the sedimentation mechanism depends upon the residence time which a particle spends in an airway and the angle of inclination of the latter with respect to the action of gravity. The Brownian motion of submicron particles due to collisions with gas molecules produces a deposition probability that is also related to the residence time in an airway. The mathematical form of a deposition efficiency formula for any specific mechanism will depend upon both the velocity profile of the airstream and the character (laminar or turbulent) of the motion, particularly as the latter affects the radial dispersion of particles in an airway.

Mathematical formulae to calculate the probability of aerosol deposition in branching networks like the human TB tree have been derived by MARTONEN (1980). The development and detailed analysis of the formulae will be the subject of another publication. The total deposition efficiency due to the action of all aforementioned mechanisms, $P(T)$, is calculated from the superposition equation

$$P(T) = P(S) + P(D) + P(I) + P(D)P(S)P(I) - P(S)P(I) - P(S)P(D) - P(D)P(I) \quad (1)$$

where the deposition probabilities of the inertial impaction, sedimentation and diffusion mechanisms are denoted as $P(I)$, $P(S)$ and $P(D)$ respectively. The superposition equation was used by LANDAHL (1950) to account for the fact that total deposition is not merely additive, because particles deposited by one mechanism are not available for deposition by another.

The probability of particle deposition from inertial impaction due to centrifugal motion at a bronchial bifurcation site in a laminar airstream is

$$P(I) = \frac{2}{\pi} \left[e(1 - e^2)^{1/2} + \arcsin(e) \right] \quad (2)$$

where $e = \pi \tau \bar{u}_i / 8r_i$. However, if the movement of air through a respiratory passage is turbulent the deposition probability must be expressed as

$$P(I) = 1 - \exp \left[-\frac{4e}{\pi} \right]. \quad (3)$$

Deposition efficiencies due to diffusion in laminar flow can be calculated using

$$P(D) = 4 \left[\frac{K}{\pi} \right]^{1/2} - K \quad (4)$$

where $K = Dl_i / \bar{u}_i r_i^2$. But, if turbulent conditions exist, then

$$P(D) = 1 - \exp \left[\frac{-0.022 D^{3/4} Re_i^{7/8} l_i}{\bar{u}_i r_i^2} \right]. \quad (5)$$

In the human TB tree conducting airways will have different angles of inclination with respect to the horizontal. The direction of airflow during inspiration may have a component aligned with the direction of action of gravity on particles in some airways, but will be acting against it in others. In the former case, termed downhill motion, the mean particle residence time spent in an airway may be formulated as

$$\bar{t}_i = \frac{l_i}{\bar{u}_i + v \sin \phi_i}. \quad (6)$$

Thus, accounting for this relative movement between an airborne particle and the surrounding airstream results in an aerosol having a reduced mean residence time in the airway. Conversely, in uphill motion the mean particle residence time in an airway is increased to the value

$$\bar{t}_i = \frac{l_i}{\bar{u}_i - v \sin \phi_i}. \quad (7)$$

The equation describing the deposition probability of the sedimentation mechanism for laminar airflow through an airway is given by equation (2) where $e = \bar{t}_i v \cos \phi_i / 2r_i$. When turbulent airflow exists the deposition probability equation becomes

$$P(S) = 1 - \exp \left[-\frac{2g\tau \bar{t}_i \cos \phi_i}{\pi r_i} \right]. \quad (8)$$

Hygroscopic aerosol behaviour in the TB tree

Equations (2)–(8) show that the parameters which characterize a spherical particle and determine its deposition probability in a given airway for a prescribed inspiratory flow rate are its density and diameter. For a hygroscopic particle these two parameters may be continuously changing throughout the TB tree because of the absorption or evaporation of water vapour. The probability of deposition within a specified airway may be calculated if the size and density of a hygroscopic particle at that location are known. The time required for an inhaled particle to reach a prescribed bronchial generation is the summation of mean residence time spent in proximal airways. If the change in particle diameter as a function of time at the prevailing temperature and relative humidity is known, the final diameter at a prescribed bronchial location can be determined. The density of the particle may then be calculated by assuming the change in size is due only to the addition of water vapour.

The experimental growth rate data in Fig. 2 for dry aerosolized drugs which are measured under simulated lung conditions can be used to model the increase of particle size with depth of penetration in the respiratory tract. Therapeutic aerosols are usually administered orally, so hygroscopic growth is assumed to start at the larynx. Since the time-span available for hygroscopic growth prior to entering a specific TB airway generation is the summation of the mean residence times spent in proximal generations, the time variable in the abscissa of Fig. 2 can easily be translated and expressed in terms of Weibel's morphology for a given inspiratory flow rate. Figure 4 shows typical growth rate data plotted in the form to be used in theoretical calculations of TB deposition; the ratio of particle D_{ae} entering a specific airway generation to its D_{ae} at the trachea is plotted using data for various 1% Isuprel® hydrochloride particle sizes.

Modelling aerosol deposition

A comparison of calculated total dose delivered to, and regional distribution within, a 16 generation TB tree was made for non-hygroscopic and hygroscopic aerosol particles. Dry particles of identical D_{ae} entered the trachea in the respective cases. The deposition of non-hygroscopic particles provides baseline data against which the effect of hygroscopic growth can be quantitated.

FIG. 4. Change in aerodynamic diameter, D_{ae} , of 1% Isuprel® hydrochloride particles in a Weibel TB tree due to hygroscopic growth. Graphs refer to dry particles entering the trachea with initial aerodynamic diameters as indicated. The inspiratory flow rate is 40 l. min^{-1} .

HILLER *et al.* (1978) measured the aerodynamic size distributions of various metered-dose bronchodilator aerosol generators. Units containing isoproterenol hydrochloride in micronized powder form had particle size distributions with a count median diameter (*CMD*) ranging from 0.62 to 0.82 μm , a *MMAD* between 2.8 and 3.9 μm and a geometric standard deviation of 1.8–2.1. Since these aerosols are generated as dry powders which contain no glycerine, their hygroscopic growth in the TB tree is assumed to be the same as the dry 1% Isuprel[®] hydrochloride particles (Fig. 2). Particles of 0.7, 3.0 and 5 μm in aerodynamic diameter were used in the following calculations of TB deposition to correspond to the typical medicinal *CMD* and *MMAD* values.

Table 1 and Fig. 5 show the deposition patterns calculated for initially dry 0.5 and 1% Isuprel[®] hydrochloride and non-hygroscopic particles of 3 μm aerodynamic diameter inhaled at 40 l. min⁻¹. D_{ae} values for the particles at generation 16, $D_{ae}(16)$, are listed. For example, a 1% Isuprel[®] hydrochloride particle enters the trachea, generation 0, with $D_{ae}(0) = 3 \mu\text{m}$ and enters the last generation of conducting airways of the TB tree with $D_{ae}(16) = 4.3 \mu\text{m}$. Aerosol deposition in the TB tree may be seen to increase with the degree of particle hygroscopicity. Tabulated data show that, for a 1% Isuprel[®] hydrochloride (without glycerine) aerosol, total TB deposition has increased about 53% relative to non-hygroscopic particles as a result of water absorption while in respiratory airways. Furthermore, the presence of glycerine itself has a pronounced influence upon the relative deposition of the Isuprel[®] hydrochloride aerosols. Removing glycerine from an Isuprel[®] hydrochloride solution raises total TB deposition from 20.2 to 29.5%, an increase of 46%. This suggests that it may be

FIG. 5. A comparison of non-hygroscopic and hygroscopic bronchodilator aerosol deposition patterns. Deposition fraction as a function of location within the TB tree is illustrated. Ordinate is the ratio of the number of particles deposited in generation i to the number entering the trachea. The inhaled particle aerodynamic diameter and inspiratory flow rate are $D_{ae}(0) = 3 \mu\text{m}$ and 40 l. min⁻¹.

TABLE 1. COMPARISON OF THE TOTAL DEPOSITION, AND REGIONAL DISTRIBUTION, OF NON-HYGROSCOPIC AND HYGROSCOPIC BRONCHODILATOR AEROSOLS IN THE TB TREE. INSPIRED DRY PARTICLE HAS $D_{ae}(0) = 3 \mu\text{m}$. TRACHEAL FLOW RATE IS 40 l. min^{-1}

Aerosol particle	Total TB deposition (% of number entering trachea) $0 \leq i \leq 16$	Regional distribution within TB tree (% of total TB deposition)		
		$0 \leq i \leq 6$	$7 \leq i \leq 10$	$11 \leq i \leq 16$
Non-hygroscopic	19.1	38.4	24.6	37.0
0.5% Isuprel® hydrochloride (with glycerine)	20.2	35.6	24.2	40.2
1% Isuprel® hydrochloride (without glycerine)	29.5	36.7	24.3	39.0

desirable to add (or remove) humectants to medicinal aerosols so as to increase the dosage of drugs actually deposited in conducting airways of patients. The influence of glycerine upon the regional distribution of particles that are deposited within the TB tree, however, is negligible for these conditions.

The importance of submicron particles in both therapeutic and toxicologic considerations of inhaled aerosols has been emphasized by MORROW (1974). Because of their presence in great numbers in the metered-dose aerosols sampled by HILLER *et al.* (1978) they are of major concern even though they may be less efficiently deposited than larger particles. The influence of inspiratory flow rate upon the distribution of dose of inhaled particles of initial $D_{ae} = 0.7 \mu\text{m}$ is shown in Fig. 6 for non-hygroscopic and 1% Isuprel® hydrochloride aerosols. At the lower flow rate of 15 l. min^{-1} both the non-hygroscopic and hygroscopic aerosols are primarily deposited in the lower

FIG. 6. The influence of inspiratory flow rate upon the deposition patterns of non-hygroscopic and hygroscopic bronchodilator aerosols. The inhaled particle aerodynamic diameter is $D_{ae}(0) = 0.7 \mu\text{m}$. Ordinate is the ratio of the number of particles deposited in generation i to the number entering the trachea.

airways owing to the efficiency of the sedimentation and diffusion mechanisms. Total deposition of the hygroscopic aerosol is greater, but the regional distribution of the deposited particles is relatively unchanged, as can be seen from the like shape of the deposition patterns. With an increase in flow rate to 60 l. min^{-1} , however, the fraction of total deposition occurring in the upper airways is significantly increased because of increased efficiency of the inertial impaction mechanism [equations (2) and (3)]. The total and dose regional distribution are presented in Table 2. Here it is shown that total deposition of the 1% Isuprel® hydrochloride aerosol is increased by 56% with respect to non-hygroscopic particles of identical inhaled aerodynamic size. It is perhaps more important to note, however, that the regional distribution has been changed. The fraction of deposited particles caught in the lower airways does not change, being about 32 and 34% for the inert and hygroscopic particles, respectively, but the fraction deposited in the upper airways changes from about 21 to 39%, an increase of about 86%. This increase occurs primarily at the expense of middle airway deposition which decreases about 42%.

Table 3 and Fig. 7 show the theoretical predictions for a $D_{ae}(0) = 5 \mu\text{m}$ NaCl particle entering the trachea at an inspiratory flow rate of 60 l. min^{-1} . Using the theoretical growth rate curve of CRIDER *et al.* (1956) at 96% relative humidity from Fig. 2, a dry NaCl particle enters the trachea with $5 \mu\text{m}$ aerodynamic diameter and enters $i = 16$ with $D_{ae}(16) = 7.9 \mu\text{m}$. The increase in aerodynamic size is only to $5.9 \mu\text{m}$ when the experimental growth data for NaCl in Fig. 2 is used to describe hygroscopic behaviour. It is evident upon comparing deposition patterns that total deposition in the TB tree increases with increasing particle hygroscopicity but that the regional

TABLE 2. COMPARISON OF THE TOTAL DEPOSITION, AND REGIONAL DISTRIBUTION OF NON-HYGROSCOPIC AND HYGROSCOPIC BRONCHODILATOR AEROSOLS IN THE TB TREE. INSPIRED DRY PARTICLE HAS $D_{ae}(0) = 0.7 \mu\text{m}$. TRACHEAL FLOW RATE IS 60 l. min^{-1}

Aerosol particle	Total TB deposition (% of number entering trachea) $0 \leq i \leq 16$	Regional distribution within TB tree (% of total TB deposition)		
		$0 \leq i \leq 6$	$7 \leq i \leq 10$	$11 \leq i \leq 16$
Non-hygroscopic	3.09	21.4	46.6	32.0
1% Isuprel® hydrochloride (without glycerine)	4.82	38.8	27.0	34.2

TABLE 3. COMPARISON OF THE TOTAL DEPOSITION, AND REGIONAL DISTRIBUTION, OF NON-HYGROSCOPIC AND HYGROSCOPIC NaCl AEROSOLS IN THE TB TREE. INSPIRED DRY PARTICLE HAS $D_{ae}(0) = 5 \mu\text{m}$. TRACHEAL FLOW RATE IS 60 l. min^{-1}

Aerosol particle	Total TB deposition (% of number entering trachea) $0 \leq i \leq 16$	Regional distribution within TB tree (% of total TB deposition)		
		$0 \leq i \leq 6$	$7 \leq i \leq 10$	$11 \leq i \leq 16$
Non-hygroscopic	52.0	52.6	26.2	21.2
NaCl (theory)	77.9	58.8	24.1	17.1
NaCl (experiment)	59.3	52.6	26.0	21.4

FIG. 7. A comparison of non-hygroscopic and hygroscopic NaCl deposition patterns. Deposition fraction as a function of location within the TB tree is illustrated. Ordinate is the ratio of the number of particles deposited in generation i to the number entering the trachea. The inhaled particle aerodynamic diameter and inspiratory flow rate are $D_{ae}(0) = 5 \mu\text{m}$ and 60 l. min^{-1} .

distribution of deposited particulate matter is relatively unchanged. Total TB deposition has increased about 50% relative to non-hygroscopic particles when the theoretical growth curve is used. The influence of the laryngeal jet upon aerosol mixing and initial hygroscopic growth and subsequent TB deposition may be determined by comparing calculations using the theoretical and experimental hygroscopic growth curves. Use of the theoretical curve for NaCl leads to a prediction of about 78% total deposition, which is about 31% greater than the corresponding calculated value using the experimental curve. Thus, assuming ideal mixing in the trachea by ignoring the laryngeal jet, as was done by MILBURN *et al.* (1957) can lead to an overestimate of TB deposition.

SUMMARY

Experimental measurements were made of the hygroscopic rates of growth of dry monodisperse aerosols of sodium chloride and Isuprel® hydrochloride, a therapeutic bronchodilator drug, under conditions simulating the gas dynamics and atmosphere of the human respiratory system. Isuprel® hydrochloride from commercially available solutions not containing glycerine grew at the same rate as sodium chloride particles. However, the addition of glycerine suppressed the growth rate. The hygroscopic growth rates have also been found to depend directly on the Reynolds number of the flow through the chamber in which increases in particle size were measured.

Calculations of total dose delivered to a human TB tree model, and its regional

distribution, show that hygroscopic growth can markedly influence deposition of aerosols. Due to particle growth an enhancement in total deposition may usually be expected relative to a non-hygroscopic particle of the same inhaled aerodynamic size. Growth and deposition calculations which are based on initially dry particles obtained from 1% Isuprel® hydrochloride solutions are useful for predicting the TB deposition of metered-dose bronchodilator aerosols from hand-held devices which contain isoproterenol hydrochloride as a micronized powder. Depending upon the inspiratory flow rate, the growth of such submicron particles by water absorption was shown to be sufficient to imply greatly increased deposition by inertial impaction in the upper bronchi. This resulted in a different regional distribution of deposited particulate matter when compared with inert particles of like inhaled aerodynamic size. The addition of glycerine to an Isuprel® hydrochloride solution significantly lessened the total quantity of aerosol deposited but did not alter its regional distribution under the conditions tested. Thus, it may be feasible to incorporate growth inhibitors or enhancers in medicines to be aerosolized in order to control the rate of hygroscopic growth and total deposition efficiency. Correctly formulating and accounting for these effects may permit medicinal aerosols to be selectively deposited at TB locations and thus improve clinical aerosol therapy procedures.

The great disparity between predicted deposition patterns for NaCl aerosols when different aerosol mixing modes are considered below the larynx indicates the importance of accurately simulating not only the lung's relative humidity and temperature environment when studying particle growth, but fluid dynamics as well. The rate of aerosol mixing which occurs in the trachea due to the entrance effect of the larynx is an important factor influencing the deposition efficiency of hygroscopic particles. The actual degree of mixing in a human will depend upon the intensity of the laryngeal jet which depends upon the inspiratory flow rate and laryngeal geometry.

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DISCUSSION

T. L. CHAN: Your model predicts no particle deposition in the trachea. This, I believe, is not unlikely in view of the experiments with lung casts described earlier (p. 169). Tracheal deposition can be easily modelled for particles in your size-range of interest by inertial deposition in a tube bend ($\eta_{tr} = 1.28$ St). This should be included in your calculations. Your statements regarding the role of the laryngeal jet on flow development in the airways are valid. My colleagues and I (CHAN *et al.*, *J. Aerosol Sci.* 1980, 11, 447–459) have shown that the laryngeal jet creates turbulence in the trachea and is responsible for a deposition 'hot-spot' distal to the larynx.

Dr MARTONEN: The influence of the larynx upon the fate of inhaled particles is quite complex. Turbulent airflow patterns are generated there which may affect the trajectories and subsequent deposition efficiencies of airborne particles in at least the trachea and first few generations of large bronchi. The theoretical model presented here attempted to account for this and losses in the trachea were negligible, because it was assumed that deposition occurred from turbulent diffusion only. Yet another effect of the larynx is that particles entrained in the laryngeal jet are directed against the trachea surface immediately downstream from the glottis opening forming the 'hot-spot' you refer to. In view of the information presented here earlier I will improve the model further simply by incorporating that experimental data into it as an empirical factor to correct for laryngeal jet impaction.

It should be noted that the experimental work you refer to concerned nonhygroscopic particles only. Here we have specifically studied the growth rates of hygroscopic aerosols in a laboratory system that simulates the temperature and relative humidity environment as well as the fluid dynamics of the upper tracheobronchial tree. Our findings demonstrate that the laryngeal jet may dictate the mode and rate of aerosol mixing in the trachea and, as a result, exert a major effect upon the behaviour of hygroscopic aerosols in the lung.

J. HEYDER: (i) In your experimental study of particle growth, the RH was below 95% to simulate the conditions of the upper tracheobronchial tree. In your calculations, however, you used these experimentally determined growth data to calculate deposition in the lower tracheobronchial system also. Could you comment?

(ii) Growth rate is particle-size dependent. In your paper, you considered only mono-disperse aerosols, but medicinal aerosols are poly-disperse. Did you look into the behaviour of the latter?

Dr MARTONEN: The RH values in our experimental system were in the 90–95% range to be consistent with published data for the trachea and large airways of human subjects. Hence, the use of our hygroscopic growth rate data in aerosol deposition efficiency calculations should be accurate for the upper tracheobronchial tree. We are not aware of any systematic mapping of relative humidity profiles throughout the tracheobronchial network, but with progression through it values probably eventually exceed 98–99%. Use of our growth rate data to describe hygroscopic aerosol behaviour in such peripheral regions, therefore, is an approximation. In future experiments we will focus on measuring growth rates at elevated relative humidities, which will permit us to more accurately formulate the action of hygroscopic particles in the deep lung.

In reference to your second question, I must note that the use of sophisticated equipment to produce monodisperse medicinal aerosols for medical research and treatment of patients is becoming more common in practice. For example, in our aerosol therapy procedures we administer monodisperse hygroscopic bronchodilator aerosols to human subjects. The aerosols are produced by a spinning top instrument. We have specifically used monodisperse aerosols thus far in our research, because we are developing techniques to be able to selectively deposit therapeutic agents within the human respiratory system. If our work schedule permits, we would like to address the problem you refer to, namely, to determine the growth rate characteristics of polydisperse aerosols, because such medicinal aerosols are commonly generated from disposable laboratory nebulizers or hand-held devices that deliver a metered dose of micronized powder.