DEVELOPMENT OF A STOCHASTIC LUNG MODEL - EXPERIMENTAL INVESTIGATION OF ENHANCED DEPOSITION AT BRONCHIAL AIRWAY BRANCHING SITES AND MONTE CARLO MODELLING OF RANDOM PARTICLE WALKS

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INTRODUCTION

Aerosol deposition calculations are commonly based on simplified models of the anatomical structure of the human lung. These lung models consist in most cases of a symmetric arrangement of straight cylindrical tubes with specified diameters, lengths, and number of airways. Morphometric studies have revealed, however, that a realistic airway system is highly asymmetric with randomly varying linear dimensions and branching angles. This paper presents preliminary results of our joint effort to develop a more realistic model for aerosol deposition in human lungs by Monte Carlo simulation techniques in close connection with detailed measurements of regional particle deposition in bifurcating airways.

AEROSOL DEPOSITION IN BIFURCATION UNITS

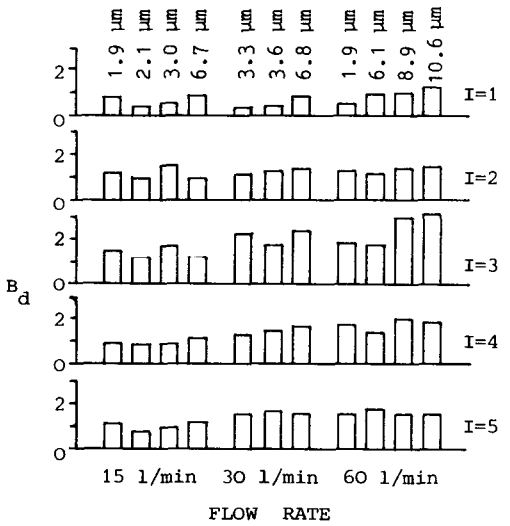
Methods

A combined larynx-TB model system, aerosol dispersion regulating apparatus, and laboratory protocols used to quantitate aerosol deposition have been discussed in detail elsewhere (1); for brevity, salient features only will be presented here. Six generation, hollow, single-pathway TB tree models were constructed from Silastic^{R} E RTV silicone rubber following the dimensions of a symmetric, dichotomously branching morphology of human conducting airways (2). Three Silastic^{R} larynx casts were made from original replica casts moulded from autopsy specimens of human larynges (3). The interior configurations of the three different casts were flow-related to constant inspiratory rates of 15, 30 and 60 l/min. The larynx casts insured that airflow patterns in downstream TB models were as physiologically realistic as possible to simulate in vivo conditions (laryngeal jet and flow instabilities created at the glottis).

Monodisperse ammonium fluorescein aerosols were produced with a spinning-top instrument. Aerosol mass median aerodynamic diameters varied from 1.9 to 10.6 μm, with geometric standard deviations between 1.11 and 1.18. Aerosol dispersion was precisely regulated with an arrangement of rotameters and vacuum pumps; airflow was divided symmetrically at each airway bifurcation. TB models were dissected into well-defined segments to quantitate deposited aerosol mass. Pieces were immersed in measured volumes of aqueous 0.1 N ammonium solution to dissolve deposited particles; aliquots of each wash were analyzed with a spectrophotofluorimeter.

Results and Dosimetry Implications

Measured localized deposits, or "hot spots", at airway branching sites are compiled in Fig. 1. Measured bifurcation doses showed two recurrent patterns. First of all, B_d values were minimum at the trachea-main bronchi junctions, and secondly, values were maximum entering airway generation 3. The I=1, 2, etc., terminology is



Bifurcation dose, B_d, is defined as:

B_d = (aerosol mass deposited within bifurcation zone/aerosol mass deposited within sister airways) (surface area of sister airways/surface area of bifurcation zone).

$B_d > 1$ indicates that a bifurcation zone has received a greater dose than if the total aerosol mass deposited in sister airways was uniformly distributed

Fig. 1 Distribution of deposited aerosol mass

in accordance with the Weibel (2) definition. Importantly, dose distributions within bifurcation zones per se were heterogeneous. Inspection of TB model interiors prior to dissection and washing revealed enhanced aerosol mass concentrations at carinal ridges (or airstream dividers) within each bifurcation zone.

Histological investigations (4, 5) have detected concentrated neoplastic and preneoplastic lesions at bifurcation sites. Therefore, the data of Fig. 1 and the very limited submicron particle findings (6, 7) suggest that TB sites, where bronchogenic carcinomas originate, may be directly related to initial sites of enhanced particle deposition. Moreover, it has been suggested (8) that mucociliary clearance rates may be slowest at airway branching sites. Epithelial cells located there could have increased exposure to inhaled aerosols of health effects concern. Together with preferential particle deposition at bifurcations originally, this latter factor may give additional support to a hypothesis that bronchogenic cancers are induced within bifurcation zones.

Sufficient experimental evidence exists that "hot particles" in the lungs are less carcinogenic than uniformly distributed alpha-emitting radionuclides. The main reason for this finding is increased cell killing by multiple alpha particle traversals in the cellular cluster around the "hot particle". In the case of "hot spots" at bronchial branching sites the number of emitted alpha particles is significantly smaller than for "hot particles" making multiple cellular hits a very unlikely event. Thus, enhanced deposition increases only the number of cells traversed, and, consequently, the probability for cancer induction.

STOCHASTIC LUNG MODELLING

Anatomical Lung Model

Current anatomical lung models do not reflect the variability of the structural components of the human lung which leads to experimentally observed random variations of particle deposition (9). To our knowledge, the most detailed morphometric

data are provided by Raabe et al. (10). In their extensive investigation, each airway segment is assigned a unique identification number which allows statistical sampling of airway parameters to construct probability distributions for each airway generation. From all data files, only the files DS 1, 8 and 10 have been selected for statistical analysis, because a) these sets contain the largest amount of data, and b) the cut-off criterion is the same in all three files.

For mean airway diameters, a "saturation value" of 0.8 mm is reached in generation 13 (Weibel morphology). Further statistical analysis of the data base suggests, however, that this finding illustrates the experimental cut-off rather than it is a realistic anatomical effect. It is interesting to note that Yeh and Schum (11) adopted a smaller saturation value of about 0.44 mm, while Weibel (2) preserved a decrease in diameter, although the curve flattens out in the peripheral airways. In Fig. 2, the coefficients of variation, i.e. the standard deviation σ divided by the mean μ, are plotted vs. the generation number (Weibel morphology) for the three files. No values were included for the first five generations, since the number of data in these generations was too small to yield statistically significant values. Up to about generation 13 a steady increase of the coefficient of variation can be observed. The following slight decrease is most probably due to the already discussed cut-off effect. For comparison, Yu et al. (12) assumed a linear relationship between coefficient of variation and generation number, starting with 0.12 for the trachea and ending with 0.24 for generation 23. Although a rigorous statistical analysis could not confirm in all cases the originally anticipated lognormal distributions, sampling from lognormal distributions will hardly be the main source of error.

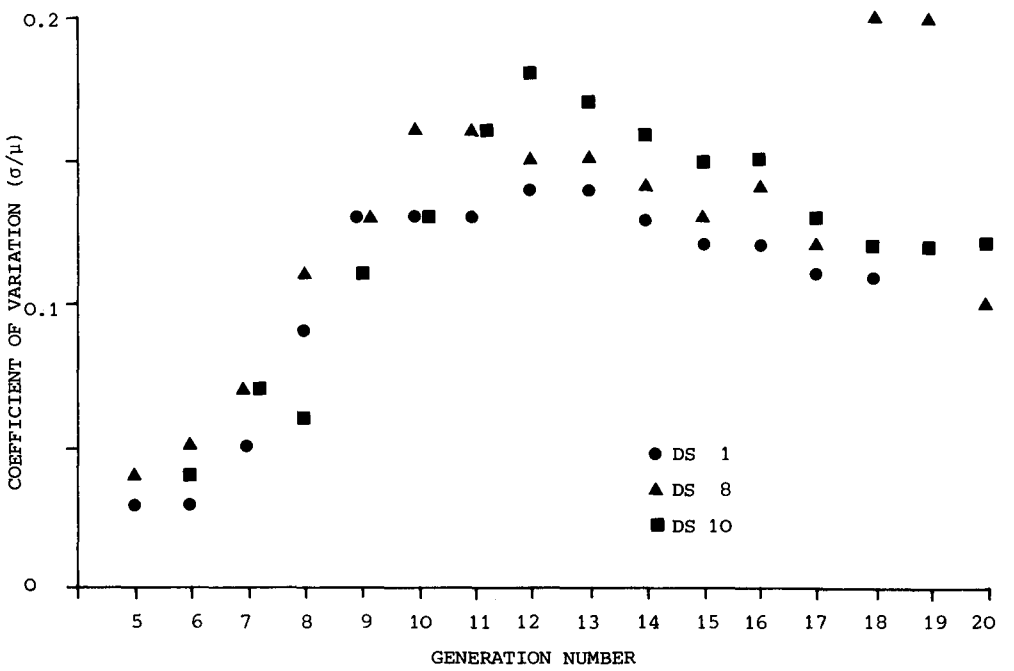


Fig. 2 Coefficients of variations for airway diameters from generations 5 through 20

A complete analysis of the morphometric data yielded further interesting results:

(a) The average ratio of the parent cross-sections to the cross-sections of both daughters is 0.82 for generations 5-16, indicating that parent and daughter dimensions are correlated.
(b) The frequency distribution of the diameter ratio of minor to major daughters, illustrating the asymmetry of branching, shows that high asymmetries are statistically related to large parent diameters.
(c) The most likely distribution of airway lengths within a defined generation is again lognormal (within the above limitations) with coefficients of variations similar to the ones found for diameters.
(d) Studies of correlation between diameters and lengths of the same generations in the same lobes revealed that the length of a tube belongs always with the highest probability to the same equiprobability class as its diameter.

Monte Carlo Random Pathway Model

The most effective method to handle complex asymmetric and statistically varying systems is stochastic modelling. For the modelling of random walks of aerosol particles during inhalation and exhalation in a random airway structure, the Monte Carlo code IDEAL was developed. For the simulation procedure, all geometrical data are selected randomly from the prespecified distributions. During the flight of the particle, time is continuously recorded and the selected dimensions are corrected for the change of the geometry during the breathing cycle by a sine function. The decision whether a particle continues its path in the major or minor daughter tube is also made by random selection. In the case of a deposition event no actual deposition of the particle is simulated; only the statistical weight attributed to the particle is decreased. The deposition probabilities for each airway generation and the exhaled fractions as a function of time are recorded at the end of each simulation.

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