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Application of an Idealized Model to Morphometry of the Mammalian Tracheobronchial Tree [1]

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ABSTRACT   Quantitative anatomical descriptions (morphometry) of the tracheobronchial airways are of importance in many applications including the preparation of successful mathematical models describing airflow patterns and deposition patterns of airborne particles in the lung. Morphometric data are also useful in studies of comparative anatomy and in describing normal and diseased states of an organ. The collection of such data is aided by the use of idealized models of airway branches of the tracheobronchial airways. Morphometric measurements from the lungs of several mammalian species are presented using a model that consists of three connected tubular segments. The morphometric model uniquely defines an identification number for each branch segment, a branching angle, an airway segment length and diameter, an inclination of a segment to gravity and the degree of alveolarization of each segment. Designed to be compatible with computerized data handling, the model is unambiguous and realistic, but flexible so that anomalous anatomical structures can be classified and noted. Morphometric data describing the variation of structure with depth in the tracheobronchial airways are presented in the form of graphical representations of anatomical measurements on replica casts of the human, dog, rat and hamster airways. These distributions describe the anatomical character of the tracheobronchial airways concisely, quantitatively, and characteristically for each species.

Interest in the mammalian respiratory tract as both a portal for entry of inhaled materials and as a primary target for several environmentally-related disease processes has provided recent impetus for improved information on the anatomy of the airways (Hanna et al., '70; International Commission on Radiological Protection, Task Group on Lung Dynamics, '66; Thurlbeck, '73). For example, development of mathematical models for predicting what fraction of and where inhaled particles will deposit require input information in three categories: aerosol physics, fluid dynamics and anatomy. The physical forces acting on airborne particles to influence their deposition must be known. The basic influences due to gravity, impaction and diffusion are relatively well understood for particle sizes most frequently seen in the industrial and urban environments. The nature of air-flow within the respiratory tract must be known, including Reynolds' numbers and primary and secondary flow patterns (Schroter et al., '69). Unfortunately, many uncertainties still exist in this area. The detailed geometry of the respiratory tract airspace, and its dynamics, must also be specified. One should know the lengths, diameters, (assuming a right circular cylindrical shape), inclinations to gravity and branch angles for all respiratory tubes.

This work concentrates on the last category, the normal anatomy of the tracheobronchial airways. The method used for quantitating airway anatomy involved making measurements on silicone rubber replica casts of mam-

malian lungs. The casting technique, performed in the closed thorax of a freshly killed animal provided casts complete to and including all terminal bronchioles. Anatomic quantitation by detailed measurements (morphometry) nessitates an unambiguous, realistic model of the basic structural units of the tracheobronchial airways. The basic unit chosen for the model, the airway branch, by definition consists of an idealized parent tubular segment, its bifurcation and two daughter segments. The terminology is similar to that used to describe binary fission of cells: i.e., a single parent cell divides to produce two offspring or daughter cells. Trifurcation or other higher-order division can, in practice, be expressed as two or more bifurcations. The airway branch is described mathematically by three groups of ordered numbers (or vectors for the segments), each group corresponding to one of the three tubular segments, parent and two daughters, comprising this structure. Each of the three groups of ordered numbers contains several numerical components in an ordered sequence. These component numbers serve to identify each segment and to quantitate geometrical parameters. The number of geometrical parameters used to describe each segment may be few or many depending on the extent of measurement and the intended application for resulting morphometric data. The measurements described here use five segment-vector components: an identification number (N), a length (L), a diameter (D), a branching angle (θ), and an inclination angle to the gravitational force (Ψ). Other parameters such as two radii of curvature (r_d and r_s) and a number indicating the fraction of the surface area of the segment that is respiratory in character (R) are also definable on the idealized model.

This idealized model and associated numerical vectors has a number of important characteristics: (a) it is continuous in that the first component of the segment vector (an identification number) identifies the segment uniquely and contains the identity of its parent, thus permitting one to connect the segment vectors into a branched structure that replicates the pattern of sequential connections in the lung; (b) it is realistic in the sense that it can closely describe geometrical characteristics of individual bifurcations occurring in mammalian lungs; (c) it attempts to define all parameters in an unambiguous

and a measurable manner (not strictly realizable for all branches); and (d) it allows for recording anomalous structure in which the idealized model is difficult to apply to the actual geometry of a lung segment.

This work, an extension of previous work by others on airway modelling, emphasizes the heterogeniety of the mammalian tracheobronchial airway. The publications by Ewald Weibel ('62, '63) established and drew attention to modern morphometry of the lung. Weibel developed, evaluated and used carefully-controlled methods for performing measurements on lung casts and on sections of lung tissue. His geometrical model of conducting airways, listing generation-by-generation, segment lengths, diameters, cross-sectional areas and volumes, has been nearly universally adopted for use in descriptive models involving air-flow and aerosol deposition calculations in the human tracheobronchial tree. This important model has some limitations in that (a) neither branching angles nor angles of inclination to gravity are provided, (b) the model does not adequately include asymmetry in daughter segment diameters, lengths and angles, and (c) due to the single-path nature of the model it does not describe differences in anatomy among lobes or even within various portions of a single lobe. What is given by the model is a mean typical path for the human conducting airways, which is convenient and perfectly adequate for many purposes.

Keith Horsfield and colleagues, working mainly with lung casts, developed data describing angles of branching and asymmetry of diameters at bifurcations in the human lung (Horsfield and Cummings, '68). Further, they developed important theoretical relationships for optimal angles of branching and for diameter ratios by mathematically minimizing both the resistance to air-flow and the volume of the conducting system.

The idealized model used here differs from these previous models of Weibel ('63) and of Horsfield and Cumming ('68) in that it uniquely identifies each tubular segment according to its diameter and a number of divisions down from the trachea, includes inclination of segments to the force of gravity, and records anomalous structural characteristics of individual bronchial segments. The model has additional applicability in fields such as endoscopy in that it provides a linked map of the tracheobronchial tree based on fea-

tures, such as diameter and branch angle, that are recognizable through the bronchial endoscope. Thus, the endoscopist can record the pathway to lesions in the tracheobronchial tree.

The present study extends our knowledge of the tracheobronchial airways in several ways. Because a flexible casting material was used, it was possible to work with essentially complete casts of the tracheobronchial airways down to and including all terminal bronchioles so large extrapolations were not necessary. Since the casts were all prepared and cured inside the thorax, branching angles of all bronchi and inclinations of tubular segments to gravity were preserved for measurement. Reliable species comparisons were possible since a single group of trained morphometrists made measurements on similarly prepared casts from four species. Also, the consistent use of a binary identification numbering system, based on daughter diameters, led to linkable data and to looking at the tracheobronchial tree as consisting of *two* distinct populations of segments. These populations, called "major" and "minor" daughters, differ distinctly from one another in their geometrical properties. The major daughters being those that tend to form main trunks of airways and the minor daughters being the smaller lateral branches. Though this paper emphasizes the model used for morphometry, results in the form of data on the airway anatomy of three species are included.

MATERIALS AND METHODS
Experimental subjects

The replica casts used in this study were made from lungs as free from respiratory disease as were available. Two human lung casts were selected from three that were made and the animals were all in excellent condition at the time of casting. The human casts used both from males each of about 80 kg in weight and aged 50 and 60 years. The younger subject had been known to smoke but no abnormalities in the lung were seen in lung sections. The older, presumably a non-smoker, had some emphysematous changes and scattered fibrosis of a severity typical for his age. Two rats (BLU, Long Evans) were used, a 4-month male weighing 315 grams and an 11-month female weighing 330 grams. Two male beagle dogs were used, one 11.6 kg in weight and 17

months of age, the other 10.3 kg and 24 months of age.

Casting method

Silicone rubber was chosen as the casting material because it has excellent replicative ability, negligible shrinkage, cures at room temperature with insignificant generation of heat, and produces a flexible, tracheobronchial cast that, when suspended, does not deform under it's own weight. The lung, in the intact animal, was prepared for casting by replacing the air within with CO_2 followed by filling with degassed physiological saline. The saline dissolves the CO_2 gas within the airways allowing for a bubble-free finished cast. Casting compound was then slowly injected through the trachea. The saline diffused out of the lung and passed out of the thorax through several small slits in the thoracic wall. After injection was completed the cast was allowed to cure in situ before it was removed and the tissue digested away. Finished casts had an overall shape that corresponded closely to the shape of the thorax. Details of the casting procedure are published (Phalen et al., '73).

Completed casts were trimmed to the level of the terminal bronchiole before being subjected to measurement. The identification of terminal bronchioles on casts was accomplished by examining the surface of the airway under low ($\times$ 10) magnification. Alveoli on the walls of airway tubes are plainly seen on the cast as small protrusions (fig. 1). The

Fig. 1 The transition from non-alveolarized tracheobronchial airways to respiratory bronchioles with alveoli budding from their walls is seen on a trimmed piece of a silicone rubber cast. Oblate blebs at terminations of airways indicate that the casting material was injected only to the level of the fourth or fifth order respiratory bronchioles. The specimen, from a dog lung cast, is about 18 mm across at its widest point. Photo by Doctor T. L. Chiffelle.

most distal airway, along any path on the cast, that did not have alveoli on its wall was called a terminal bronchiole. This working definition proved to be unambiguous in that the data from two morphometrists measuring the same lobe usually yielded the same number of divisions to the terminal bronchiole. The validity of this definition of a terminal bronchiole on a cast is supported by the fact that when our data for the entire human lung are combined, the mean number of generations in the tracheobronchial tree is 16 (trachea = 1) just one less that determined by extrapolation by Weibel ('63). Weibel gives diameter and length values of 0.60 and 1.65 mm respectively for the adult terminal bronchiole from sections corresponding to an estimated lung inflation of "3/4 total lung capacity." Our mean values from casts, 0.62 mm for diameter and (fig. 1) 1.72 mm for length, are not significantly different. The structure identified as a terminal bronchiole on our casts is apparently essentially identical to that identified as a terminal bronchiole on histologic sections.

Casts prepared in this manner were evaluated using a quantitative radiographic technique (Yeh et al., '75) and found to represent an end-inspiratory state of inflation. Branching angles, airway lengths and airway diameters were accurately preserved on the casts.

Idealized model

The segment vector is expressed as (N, L, D, θ, Ψ, R) and a symbol for description of structural anomalies. The first component of the segment vector (N) is a binary identification number that describes the location of the segment within the branching system (fig. 2). It is derived by designating the trachea as number 1 and then by attaching either a 1 or 2 to this number to obtain the identification numbers for the trachea's two daughters. Thus, 11 is the identification number for the major daughter (usually the right mainstem bronchus in humans, larger diameter) and 12 is the identification number for the minor daughter (left mainstream bronchus, smaller diameter). Likewise, the identification numbers of all other segments are derived by attaching a 1 or 2 to the right of the identification number of their parent as the daughter has the larger or smaller diameter of the pair respectively. In case both daughters have equal diameters, greater segment length, smaller branch angle or relative magnitude of another geometrical parameter may be used to distinguish major
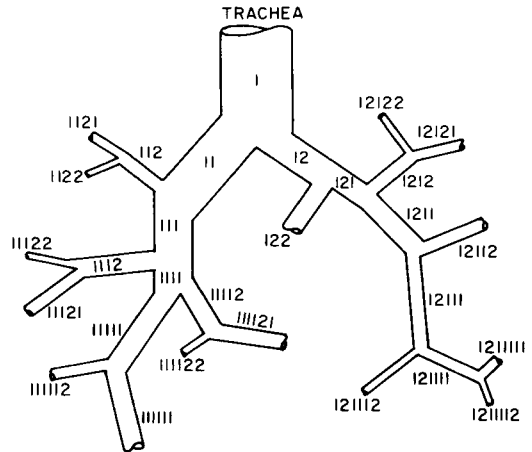

Fig. 2 Binary identification numbering system used in morphometry of the tracheobronchial tree. This system, adapted from an alphabetic scheme described by Weibel ('63) assigns a unique number to each segment and allows data to be properly linked.

from minor. The identification number for any segment thus contains the identification numbers for all segments leading from it to the trachea. Given an identification number, the corresponding segment may be located on a lung cast or during endoscopy by tracing a path to it starting at the trachea and progressing through the major or minor daughter branches depending on whether the next digit in the identification number sequence is a 1 or a 2. Also, given any branch, one can construct its identification number by tracing the path between it and the trachea. This unambiguous identification of tracheobronchial segments constitutes a system of nomenclature that has potential usefulness beyond its application to lung morphometry. This numbering system is similar to that described by Weibel ('63) using A's and B's to distinguish between two daughter segments, but different in that it is numerical and systematically applied to morphometric measurements and model construction.

The second vector component, segment length (L) may be defined in several ways. The definition selected depends upon the specific application for the data. One definition useful in particle deposition calculations is shown on figure 3. The length of a segment is defined by points a and b which fall midway between the intersections of the axes of the two daughter segments and the central axis of the parent segment. The total path length followed by an inhaled particle, for example, is represented

by the summation of individual lengths of tubes it passes through. This definition, or any other, does not lend itself to curved branches and may be quite awkward in some specific cases. In this event, notation of a length anomaly, (that will be described) to indicate length could not be measured is useful.

The diameter (D) of a segment, the third component of the descriptive segment vector, may be taken as the mean diameter of the segment averaged along the entire length. For segments with noncircular cross section, an estimate of the equivalent diameter (length $\times \pi \times \frac{(\text{equ. diam})^2}{4}$ = segment volume) is useful when the flow of air is of interest. More simply, two or three measurements of diameter along a tube are averaged to yield (D).

The branching angle (θ) of the daughter segment is defined as the change in direction of the bulk air-flow moving from the parent segment into the daughter segment (fig. 3). Again, significantly curved branches require that an angle anomaly description be attached to the segment vector.

The inclination of the segment to gravity (Ψ) is the angle between the bulk air flow direction during the inspiration of air and the force of gravity when the lung is positioned in the attitude it normally occupies in a standing animal. A vertical segment has an angle to gravity of 0° for air flowing down on inspiration and an angle of 180° for upflow during expiration. A horizontal segment has a gravity angle of 90°.

The final component (R) in the segment vector describes the percentage of surface area of the segment that is covered with respiratory structures. The alveolar structures are seen on the airway cast as small protrusions a fraction of a millimeter in size. In our studies, this parameter is entered as 1, 2, 3, or 4 depending on whether 1-25%, 25-50%, 50-75%, or 75-100%, respectively, of the segment surface is covered with alveolar protrusions. For some purposes, this classification of R into quartiles may not be precise enough. Segments with alveolar structures can be identified as either respiratory bronchioles, alveolar ducts, alveolar sacs, or in some cases, ventilatory shunts.

Radii of curvature of the flow divider or apex of the bifurcation of a segment (r_d) and curvature of the segment tube itself (r_s), if desired, are measured on lung casts with a circle template and recorded as numerical components of the segment vector. Measurement of
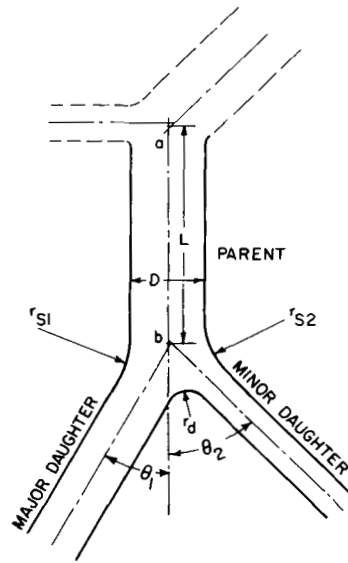

Fig. 3   The airway branch, the basic unit of structure in the idealized model of the tracheobronchial tree. Diameters, lengths, angles and radii of curvature are defined by this diagram.

radii of curvature requires considerable skill and has not yet been included in our morphometric measurements.

The above components of the segment vector are useful in particle deposition and air flow calculations but other measurements may be devised as desired.

Situations arise in morphometry when the idealized model cannot be superimposed on a real segment. That is, the actual airway segment has a structure that deviates significantly from the idealized model. In these cases, the segment vector component affected may be replaced by a blank field (for computer applications) and a description of the anomaly appended to the segment vector. We have found it convenient to devise a coding system for anomalies so that those anomalies commonly seen on our casts can be described by a single symbol. For example, anomaly code A is used in cases where the segment is not straight and, hence, the length is not easily measured. In a typical case, the segment vector might be written as follows:

(1221121, −, 0.6 mm, 30°, 45°, 2), A

Examples of anomaly codes and their frequencies of observation on an airway casts of the human are given in table 1.

A major purpose of this conceptual model is to allow the recording of anatomical data in

TABLE 1

Anomaly codes

Code	Definition	Frequency of occurrence
A	Segment has a significant radius of curvature, i.e., walls not parallel	< 10%
B	Segment has a grossly noncircular cross section	< 3%
C	Segment has one or more narrow regions, i.e., "throats"	For segment diameter > 2 mm in human, 10-20%; rest and other species < 10%
D	Segment has no well-defined angle of branching	< 10%
E	Segment has no well-defined length	< 10%
F	Segment is incomplete, either due to incomplete casting, breakage or trimming	[1]
G	Another anomaly, not included in A-F, which is described in words or a diagram on the original morphometry data sheet	< 10%
H	Diameter is much smaller with respect to parent diameter. Length recorded based on actual length, not as in idealized model from center of parent segment	< 5%
T	Segment is terminal segment on cast after trimming and identified as terminal bronchiole	[1]
U	Segment is on path to other lobes not measured in this set	[1]
X	Segment diameter is less than a specified cutoff diameter or not sampled, and therefore its daughters are not measured	[1]

[1] For any dichotomous (regular or irregular) branching tree
$$N(F, T, U, X) = 1/2 \ (N_T + 1)$$
where N_T = total number of segments
$N(F, T, U, X)$ = number of segments with code either F, T, U and/or X.

forms that can be used in computational models for predicting particle deposition and air flow within the lung. To effectively use this approach, one must be able to superimpose abstractly the idealized model and the real lung segments (fig. 4) and then make measurements on the real segment corresponding to parameters defined by the conceptual model. In practice, this usually can be done provided care is taken and proper measuring instruments are used. A good collection of measuring tools including dividers, calibrated scales, magnifying optical comparators with reticles, circle or arc templates and protractors is necessary for making reliable measurements. We have used this idealized model approach for morphometry and in about two years five morphometrists have generated about 40,000 segment vectors using lung casts from the rat, hamster, dog, and human. Agreement among morphometrists has been better than 10% (standard deviation) for lengths and diameters and within ± 10° (s.d.) for angles. The average number of airway branches (generations or, more preferably, divisions down) from the trachea to and including the terminal bronchiole are shown in table 2 for the human, dog, rat and hamster. Agreement between individual morphometrists in this average number is within ± 1 division when

TABLE 2

Average number of airway segments from the trachea to and including terminal bronchiole for each lobe in the human, dog, rat and hamster. The trachea is segment number one

Lobe	Species			
	Human	Dog	Rat	Hamster
R.A.-R.U.	15	17	13	11
R.C.-R.M.	15	19	15	13
R.I.		18	17	15
R.D.-R.L.	17	22	20	18
L.A.-L.U.	15	18	12	11
L.D.-L.L.	16	21	16	16

R.A., right apical; R.U., right upper
R.C., right cardiac; R. M., right middle
R.I., right intermediate
R.D., right diaphragmatic; R.L., right lower
L.A., left apical; L.U., left upper
L.D., left diaphragmatic; L. L., left lower

various people measure the same lobe. The raw morphometry data have been assembled in a limited-printing report (Raabe et al., '76).

RESULTS AND DISCUSSION

Upon gross examination the trimmed casts fell into two types, the human casts were roughly spherical and exhibited a relatively symmetric branching system. Casts from dogs and rats were strikingly monopodial in nature and tended to have long, tapering major bronchial pathways with short lateral branches at-
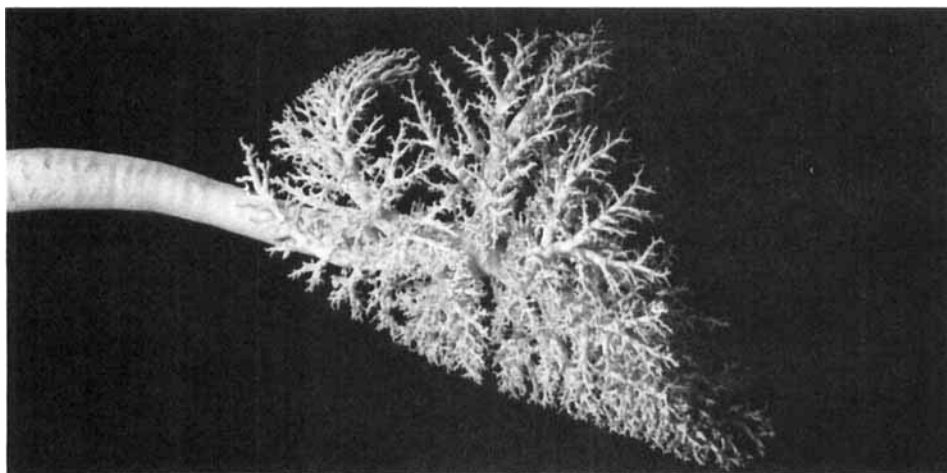
DOG
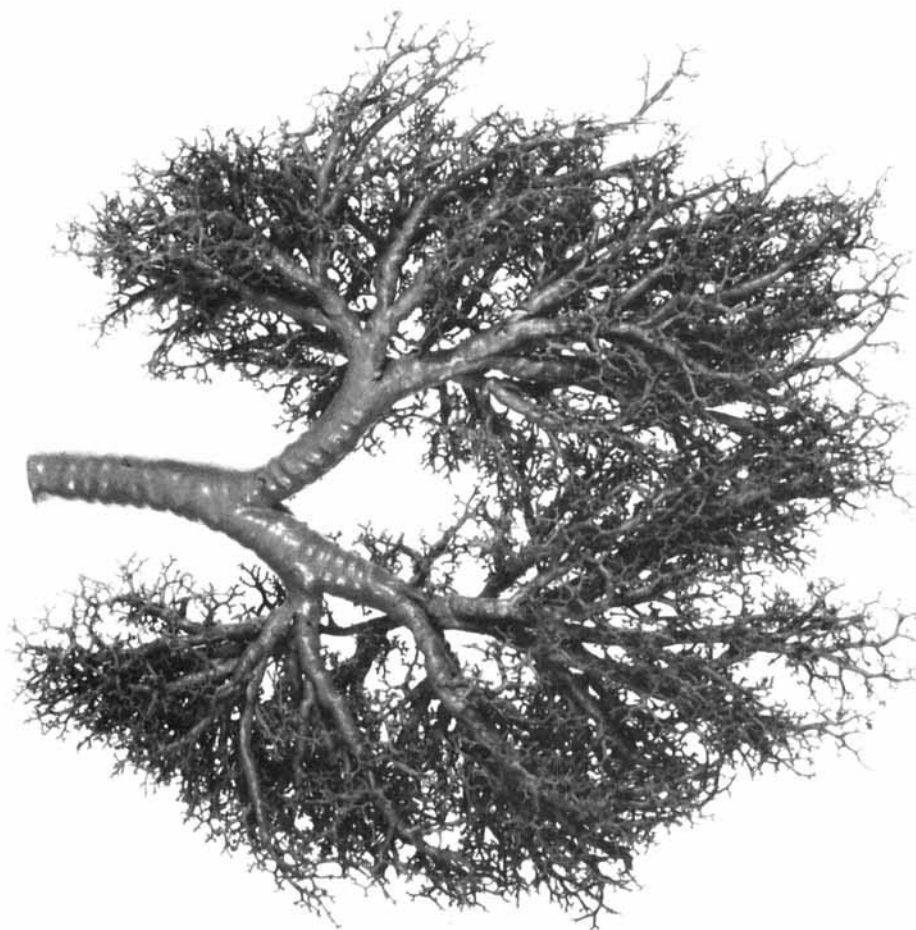
HUMAN

Fig. 4 Airway casts of the complete tracheobronchial tree from a human and a Beagle dog. The silicone rubber casts prepared in the thorax were hand trimmed to remove airways containing alveoli in their walls.
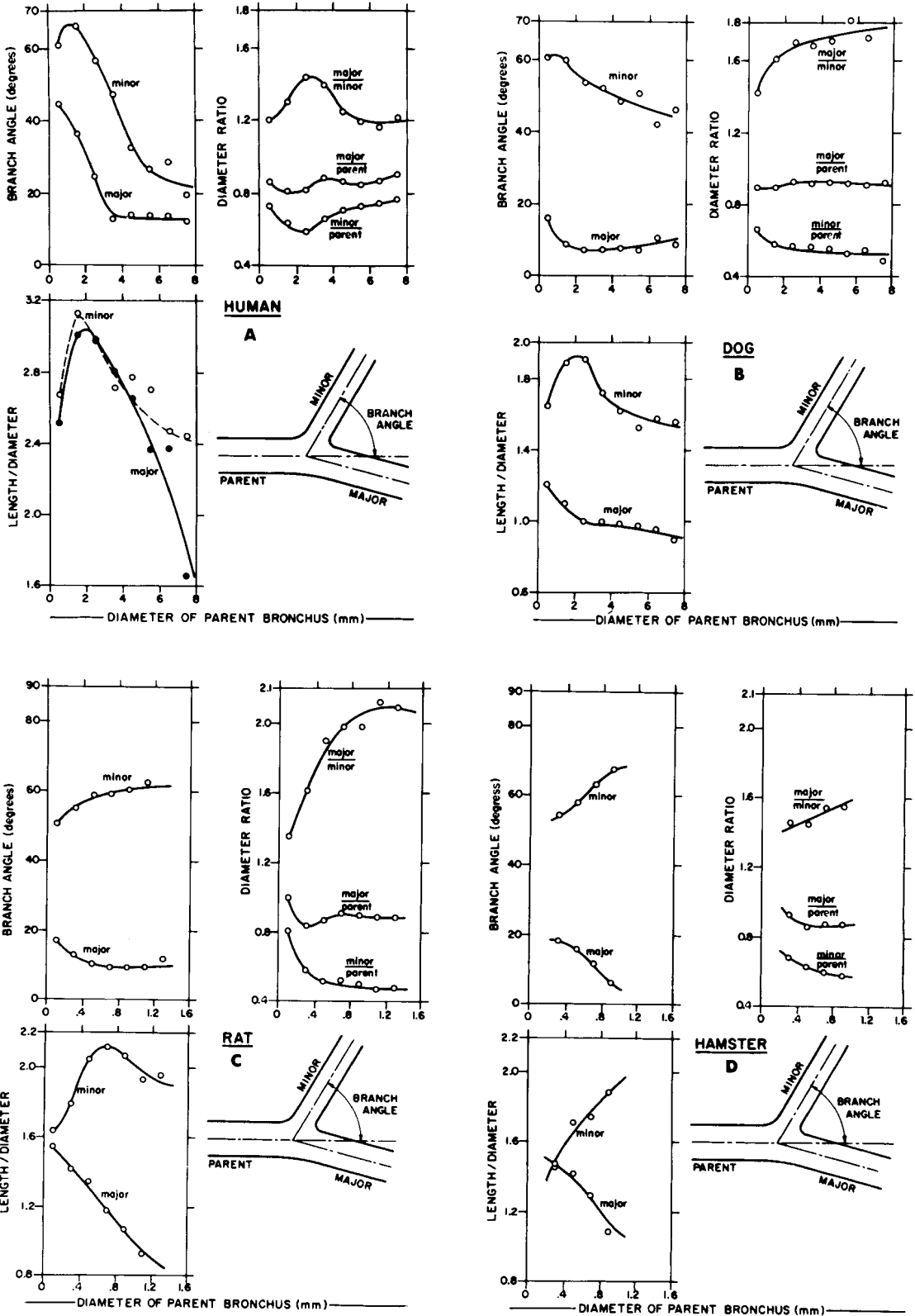
Fig. 5   Airway morphology as a function of diameter of the parent bronchus in four species: A, human; B, dog; C, rat and D, hamster. Portions of this figure reproduced with permission of the British Occupational Hygiene Society.

taching at relatively large angles. Bronchi of dogs and rats were usually short in relation to their length when compared to human bronchi. The transition from smooth (nonalveolarized) airways to those with alveoli in their walls was abrupt in the rat, but gradual in the human and dog where two to five orders of respiratory bronchioles were present.

Morphometric data from human, dog, rat, and hamster tracheobronchial casts have been plotted as mean values of the segment vector components and of several derived parameters (e.g., ratio of lengths/diameters for segments). Data describing the variation in such parameters with depth in the lung are shown in figure 5. When data are so organized, each type of lung is characterized by these sets of grouped data. For example, mean values of branch angles for the major and minor daughters (θ_1 and θ_2) imply that branch angles are nearly equal at a bifurcation in the human. The distributions for the rat, hamster and dog, however, show that their branching is monopodial. That is, the major daughter tends to branch off of its parent at a small angle while the minor daughter usually branches at a much larger angle. Such graphical representations can be used to quantify structural relationships that have previously been only verbally described. Describing the tracheobronchial airways with such statistical representations expresses both the complexity and the basic form of this structure in a concise and useful manner. This method of representing the tracheobronchial airways is a departure from the models of a single simplified structure that repeats itself while getting smaller at each division until the terminal bronchioles are reached.

Changes in lung geometry during breathing are important in many applications. They may be incorporated into this model by the use of time-variable multipliers associated with components of the segment vector. For example, the cyclic changes in an airway diameter of a given size during breathing might be simulated by multiplying the diameter by a periodic function with appropriate amplitude, shape and frequency.

These results can, in part, be compared with those for humans of Weibel ('63) and of Horsfield and Cumming ('67). Weibel gave sixteen as the generation number of the terminal bronchiole (Weibel, '63). Our data (table 2) indicate that this value is acceptable as an overall average for the human lung, but is an overestimate for upper and an underestimate

for lower lobes. Weibel published a mean length to diameter ratio of 3.1 for human segments. We find this ratio for segments in the diameter range of about 1-2 mm; outside of this range, our values are lower. Furthermore, Weibel's assumption of regular symmetric branching is less valid for large segments and more correct with respect to small airways. Horsfield's optimal branching angle of about 37.5° is most commonly observed in airways having diameters between about 3 and 4 mm, the theoretical value being too low for smaller airways and too high for larger ones. Similarly, his optimal diameter ratio for daughters, 0.76, is frequently seen for segments in only two diameter ranges, 1-2 mm and 4-5 mm. In general, these previous models appear to represent accurate overall averages for the entire human tracheobronchial airways. However, the mammalian tracheobronchial airway is more heterogeneous in geometrical structure than is implied by the older models.

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