Applied Respiratory Physiology

2nd Edition

J. F. NUNN

Applied Respiratory Physiology

2nd Edition

J. F. NUNN

M.D., Ph.D., F.F.A., R.C.S. (Eng.)

Head of Division of Anaesthesia, Medical Research Council Clinical Research Centre; Honorary Consultant Anaesthetist, Northwick Park Hospital, Middlesex. Formerly Professor of Anaesthesia, University of Leeds.

BUTTERWORTHS
LONDON–BOSTON
Sydney–Wellington–Durban–Toronto

The Butterworth Group

United Kingdom London	Butterworth & Co (Publishers) Ltd 88 Kingsway, WC2B 6AB
Australia Sydney	Butterworths Pty Ltd 586 Pacific Highway, Chatswood, NSW 2067 Also at Melbourne, Brisbane, Adelaide and Perth
South Africa Durban	Butterworth & Co (South Africa) (Pty) Ltd 152–154 Gale Street
New Zealand Wellington	Butterworths of New Zealand Ltd 26-28 Waring Taylor Street, 1
Canada Toronto	Butterworth & Co (Canada) Ltd 2265 Midland Avenue, Scarborough, Ontario, M1P 4S1
USA Boston	Butterworths (Publishers) Inc 19 Cummings Park, Woburn, Mass 01801

First edition 1969
First reprint 1971
Second reprint 1971
Third reprint 1972
Fourth reprint 1975
Second edition 1977

ISBN 0 407 00060 7

Library of Congress Cataloging in Publication Data

Nunn, John Francis.
Applied respiratory physiology.

First ed. published in 1969 under title: Applied respiratory physiology with special reference to anaesthesia.

Bibliography: p. 473
Includes index.
1. Respiration. 2. Anesthesia. I. Title.

[DNLM: 1. Respiration. WF102 N972a]
QP121.N75 1977 612.2'024'617 76-54340
ISBN 0-407-00060-7

Printed in England by the Whitefriars Press Ltd., London and Tonbridge

Contents

Chapter 1 Physical and Morphological Features of Gas Exchange and Non-respiratory Functions of the Lung

The Gas Laws
Lung Volumes and Capacities
Relation of Pulmonary Structure to Function
Non-respiratory Functions of the Lung

A knowledge of physics is more important to the understanding of the respiratory system than of any other system of the body. Not only gas transfer, but also ventilation and perfusion of the lungs occur largely in response to physical forces, with vital processes playing a less conspicuous role than is the case, for example, in brain, heart or kidney. It will therefore be clear that much of this book is concerned with physics, and it seems best to start with a brief review of those aspects which are most relevant to the behaviour of gases in the respiratory system. This is followed by an account of the structural aspects of the lungs, which is the only valid starting point for a consideration of function.

Physical quantities and units of measurement are perennial sources of confusion in respiratory physiology. Apart from any inherent difficulty, we suffer from an unnecessary duplication of units, particularly those of pressure. Appendices A and B are intended to resolve some of these difficulties but they need not be read by those readers who have already obtained a grasp of the subject.

THE GAS LAWS

Certain physical attributes of gases are customarily presented under the general heading of the gas laws. These are of fundamental importance in respiratory physiology.

Boyle's law describes the inverse relationship between the volume and absolute pressure of a perfect gas at constant temperature:

$$PV = K \qquad \ldots (1)$$

where P represents pressure and V represents volume. At temperatures near their boiling point, gases deviate from Boyle's law. At room temperature, the deviation is negligible for oxygen and nitrogen and is of little practical importance for carbon dioxide or nitrous oxide. Anaesthetic vapours show substantial deviations.

Charles' law describes the direct relationship between the volume and absolute temperature of a perfect gas at constant pressure:

$$V = KT \quad \ldots (2)$$

where T represents the absolute temperature. There are appreciable deviations at temperatures immediately above the boiling point of gases. Equations (1) and (2) may be combined as follows:

$$PV = RT \quad \ldots (3)$$

where R is the universal gas constant, which is the same for all perfect gases and has the value of 8·1314 joules/degree kelvin/mole. From this it may be derived that the mole volume of all perfect gases is 22·4 litres at STPD. Carbon dioxide and nitrous oxide deviate from the behaviour of perfect gases to the extent of having mole volumes of 22·2 litres at STPD.

Van der Waals' equation is an attempt to improve the accuracy of equation (3) in the case of non-perfect gases. It makes allowance for the finite space occupied by gas molecules and the forces which exist between them. The Van der Waals equation includes two additional constants:

$$(P + a/V^2)(V - b) = RT \quad \ldots (4)$$

where a corrects for the attraction between molecules and b corrects for the volume occupied by molecules. This expression is of particular interest to anaesthetists since the constants for anaesthetic gases are related to their anaesthetic potency (Wulf and Featherstone, 1957).

An alternative method of correction for non-ideality is to express equation (3) in the following form:

$$PV/RT = Z \quad \ldots (5)$$

For a perfect gas, Z equals unity. For a particular gas at a particular temperature and pressure, the non-ideality may be expressed as the special value for Z (usually less than unity) which may be obtained from tables.

Since Z has a special value for each gas at each temperature and pressure, useful tables of Z values are necessarily very cumbersome. It is therefore much more convenient to replace Z with a power series as follows:

$$PV/RT = 1 + B/V + C/V^2 + \ldots \quad \ldots (6)$$

The constants B, C, etc., are known as virial coefficients and vary only with temperature for a particular gas. Compilations are therefore simplified and the serious student is referred to Dymond and Smith (1969) or to Kaye and Laby (1966) which is more generally available but less complete. Values for B may be positive or negative and it is seldom necessary to use more than the one coefficient.

Adiabatic heating. A great deal of respiratory physiology can fortunately be understood without much knowledge of thermodynamics. However, a recurrent problem is the heating which occurs when a gas is compressed. This effect is sufficiently large to be a readily detectable source of error in such techniques as the body plethysmograph (page 6), and the use of a large rigid container as a simulator for the paralysed thorax.

Henry's law describes the solution of gases in liquids with which they do not react. It does not apply to vapours which, in the liquid state, are infinitely miscible with the solvent (e.g. ether in olive oil) (Nunn, 1960b). The general principle of Henry's law is simple enough. The number of molecules of gas dissolving in the solvent is directly proportional to the partial pressure of the gas at the surface of the liquid, and the constant of proportionality is an expression of the solubility of the gas in the liquid. This is a constant for a particular gas and a particular liquid at a particular temperature but usually falls with rising temperature.

For many people, confusion arises from the multiplicity of units which are used. For example, when considering oxygen dissolved in blood, it has been customary to consider the amount of gas dissolved in units of vols per cent (ml of gas (STPD) per 100 ml blood) and the pressure in mm Hg. Solubility is then expressed as: vols per cent/mm Hg, the value for oxygen in blood at 37° C being 0·003. However, for carbon dioxide in blood, we tend to use units of mmol/l of carbon dioxide per mm Hg. The units are then: mmol l^{-1} mm Hg^{-1}, the value for carbon dioxide in blood at 37° C being 0·03. Both vols per cent and mmol/l are valid measurements of the quantity (mass or number of molecules) of the gas in solution and are interchangeable with the appropriate conversion factor.

Physicists are more inclined to express solubility in terms of the *Bunsen coefficient.* For this, the amount of gas in solution is expressed in terms of volume of gas (STPD) per unit volume of solvent (i.e. one-hundredth of the amount expressed as vols per cent and the pressure is expressed in atmospheres.

Biologists, on the other hand, prefer to use a related term—the *Ostwald coefficient.* This is the volume of gas dissolved, expressed as its volume under the conditions of temperature and pressure at which solution took place. It might be thought that this would vary with the pressure in the gas phase, but this is not so. If the pressure is doubled, according to Henry's law, twice as many molecules of gas dissolve. However, according to Boyle's law, they would occupy half the volume at double the pressure. Therefore, if Henry's and Boyle's laws are obeyed, the Ostwald coefficient will be independent of changes in pressure at which solution occurs. It will differ from the Bunsen coefficient only because the gas volume is expressed as the volume it would occupy at the temperature of the experiment rather than at 0° C. Conversion is thus in accord with Charles' law and the two coefficients will be identical at 0° C. This should not be confused with the fact that, like the Bunsen coefficient, the Ostwald coefficient falls with rising temperature.

The partition coefficient is the ratio of the number of molecules of gas in one phase to the number of molecules of gas in another phase when equilibrium between the two has been attained. If one phase is gas and another a liquid, the liquid/gas partition coefficient will be identical to the Ostwald coefficient. Partition coefficients are also used to describe partitioning between two media (e.g. oil/water, brain/blood, etc.). At the time of writing, it is too early to say when SI units will come into general use for expression of solubility (*see* Appendix A). The coherent unit is millimole $litre^{-1}$ $kilopascal^{-1}$.

Graham's law of diffusion governs the influence of molecular weight on the diffusion of a gas through a gas mixture. Diffusion rates through orifices or through porous plates are inversely proportional to the square root of the molecular weight. This factor is only of importance in the gaseous part of the

pathway between ambient air and the tissues, and is of limited importance in the whole process of 'diffusion' as understood by the respiratory physiologist.

Dalton's law of partial pressure states that, in a mixture of gases, each gas exerts the pressure which it would exert if it occupied the volume alone. This pressure is known as the partial pressure (or tension) and the sum of the partial pressures equals the total pressure of the mixture. Thus, in a mixture of 5 per cent CO_2 in oxygen at a total pressure of 101 kPa (760 mm Hg), the carbon dioxide exerts a partial pressure of 5/100 x 101 = 5·05 kPa (38 mm Hg). In general terms:

$$P_{CO_2} = F_{CO_2} \times P_B^*$$

(Note that fractional concentration is expressed as a fraction and not as a percentage: per cent concentration = F x 100.)

In the alveolar gas at sea level, there is about 6·2 per cent water vapour, which exerts a partial pressure of 6·3 kPa (47 mm Hg). The available pressure for other gases is therefore (P_B − 6·3) kPa or (P_B − 47) mm Hg, an expression which recurs frequently in the following pages.

Tension is synonymous with partial pressure and is applied particularly to gases dissolved in a liquid such as blood. Molecules of gases dissolved in liquids have a tendency to escape, but net loss may be prevented by exposing the liquid to a gas mixture in which the tension of the gas exactly balances the escape tendency. The two phases are then said to be in equilibrium and the tension of the gas in the liquid is considered equal to that of the tension of the gas in the gas mixture with which it is in equilibrium. Thus a blood P_{CO_2} of 5·3 kPa (40 mm Hg) means that there would be no net exchange of carbon dioxide if the blood were exposed to a gas mixture which had a P_{CO_2} of 5·3 kPa (40 mm Hg). Directly or indirectly this forms the basis of all methods of measurement of blood P_{CO_2} and P_{O_2} (pages 372 and 441).

It is not the intention to discourse on physics any more than is necessary for the understanding of what follows in the rest of this book. Physics as applied to respiratory physiology and anaesthesia has been presented in *Physics for the Anaesthetist* (MacIntosh, Mushin and Epstein, 1958) and *Physics Applied to Anaesthesia* (Hill, 1972), which will also serve as an introduction to more advanced reading such as *The Physics of Gases*, by Radford (1964).

LUNG VOLUMES AND CAPACITIES

The lung volume is considered in relation to three volumes which are relatively fixed for a particular patient under particular conditions.

1. *Total lung capacity* (TLC), which is the volume of gas in the lungs at the end of a maximal inspiration.
2. *Functional residual capacity* (FRC), which is the volume of gas in the lungs at the end of a normal expiration. In the unconscious patient, the FRC is defined as the volume of gas in the lungs when there is no inspiratory or expiratory muscle tone and when the alveolar pressure equals the ambient pressure.
3. *Residual volume* (RV), which is the volume of gas in the lungs at the end of a maximal expiration.

* Abbreviations and symbols are listed in Appendix C.

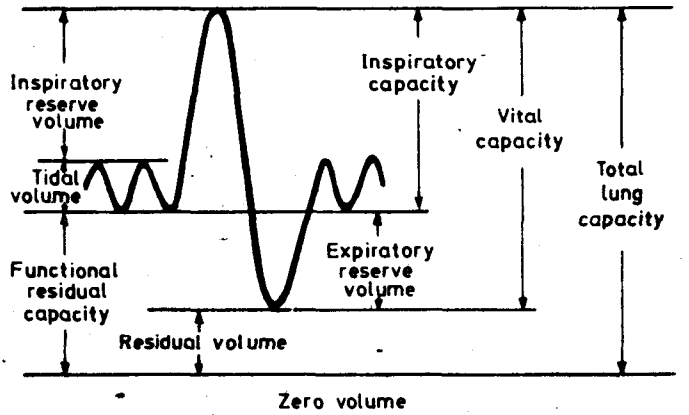

Figure 1. Static lung volumes. The 'spirometer curve' indicates the lung volumes which can be measured by simple spirometry. These are the tidal volume, inspiratory reserve volume, expiratory reserve volume, inspiratory capacity and vital capacity. The residual volume cannot be measured by observation of a simple spirometer trace and it is therefore impossible to measure the functional residual capacity or the total lung capacity without further elaboration of methods. Dynamic measurements of maximal breathing capacity and forced expiratory volume are discussed at the end of Chapter 4

Within this framework, there is no difficulty in defining inspiratory and expiratory reserve volumes, tidal volume, vital capacity and inspiratory capacity. This is best shown diagrammatically (*Figure 1*).

The total lung capacity is reached when the force developed by the inspiratory muscles is exactly balanced by forces opposing and resisting expansion. *Expiratory* muscles are contracting strongly at the end of a maximal inspiration. Inspiratory capacity may be limited either by weakness of contraction of inspiratory muscles or by diminished mobility of the lungs, chest wall or diaphragm.

There has been doubt about the precise factors governing the residual volume but it is clearly determined by the balance between the force exerted by the expiratory muscles and the resistance to decrease in volume provided by lungs, chest wall and diaphragm.

The functional residual capacity is usually considered to be dependent upon the balance of elastic forces and is considered in detail in Chapter 3. It is altered by changes in posture, alveolar pressure (relative to ambient) and development in tone of either inspiratory or expiratory muscles. It is also altered by changes in abdominal pressure (e.g. due to pregnancy) or by changes in elasticity of lungs or chest wall. Thus destruction of lung tissue in emphysema causes loss of elastic recoil and increase in functional residual capacity. It has recently been shown that anaesthesia is generally associated with a decrease in FRC and this is considered in some detail on pages 67 *et seq.*

Principles of measurement of lung volumes

Tidal volume, vital capacity, inspiratory capacity, inspiratory reserve volume and expiratory reserve volume can all be measured by simple spirometry without the

necessity of using a spirometer designed for high frequency response or low inertia. Of these measurements, only the tidal volume has any significance in the unconscious patient.

Total lung volume, functional residual capacity and residual volume all contain a fraction (the residual volume) which cannot be measured by simple spirometry. However, if one is measured, the others can be easily derived since the volumes which relate them can be measured by simple spirometry. Measurement of FRC can be made by one of three techniques. The first method is to wash the nitrogen out of the lungs by several minutes of oxygen breathing with measurement of the total quantity of nitrogen eliminated. Thus if 4 litres of nitrogen are eliminated and the initial alveolar nitrogen concentration was 80 per cent it follows that the initial volume of the lung was 5 litres. The second method uses the wash-in of a tracer gas such as helium. If 50 ml of helium is introduced into the lungs and the helium concentration is then found to be 1 per cent it follows that the volume of the lung is 5 litres. In practice, the patient's alveolar gas is allowed to equilibrate with gas in a closed-circuit spirometer circuit which contains a known concentration of helium. The resultant fall in helium concentration is a function of the FRC in relation to the volume of the spirometer circuit. It is possible to avoid the necessity of measuring the volume of the spirometer circuit by the following routine:

1. Prime the spirometer circuit with helium to give a helium concentration of He_1.
2. Draw a known volume of gas (V) into the spirometer and after equilibration note the new reduced helium concentration He_2.
3. Allow the patient's alveolar gas to equilibrate with the spirometer and after equilibration note the final helium concentration He_3.

The following expression indicates the FRC:

$$V . He_1(He_2 - He_3)/He_3(He_1 - He_2)$$

appropriate corrections being made for apparatus dead space and for temperature. FRC is normally expressed under conditions of body temperature and pressure, saturated with water vapour (BTPS).

Helium concentrations are usually measured with a catharometer and corrections are required for the presence of anaesthetic vapours. Anaesthesia with or without paralysis requires considerable modifications of technique but the problems are not insuperable (Hewlett et al., 1974a).

The third method of measurement of functional residual capacity uses the body plethysmograph making use of Boyle's law (DuBois et al., 1956). The subject is confined within a gas-tight box so that changes in the volume of his body may be readily determined as a change in either the gas volume or pressure within the box. He then adjusts his lung volume to FRC, purses his lips around a tube leading to a manometer and attempts to breathe against the occluded airway. This is rather like a Valsalva or Müller manoeuvre except that occlusion is not at the glottis but within the external breathing apparatus at a point distal to the manometer. Changes in alveolar pressure are recorded during the obstructed breathing together with the changes in lung volume which result from the pressure changes. The lung volume changes are measured as changes in whole body volume which are considered to be the same as lung volume changes under these conditions. These data permit calculation of the lung volume and the

method is both accurate and convenient. Clearly there are formidable difficulties in applying this technique to anaesthetized patients, but it has been used under these conditions in the important study by Westbrook et al. (1973) considered in Chapter 3.

RELATION OF PULMONARY STRUCTURE TO FUNCTION

This section is not intended as an exposition of lung structure but is rather an account of those structural features which are directly relevant to an understanding of function. During recent years there has been a regrettable tendency for pulmonary structure and function to be pursued as separate subjects. It is now generally realized that a full understanding of function is not possible without a morphological background.

An excellent introduction to pulmonary structure in relation to function has been written by Staub (1971). There are major reviews by Krahl (1964) and Weibel (1964, 1973). Source books are *The Lung* (Miller, 1947), *The Human Lung* (von Hayek, 1960), *The Human Pulmonary Circulation* (Harris and Heath, 1962) and *Morphometry of the Human Lung* (Weibel, 1963). The Ciba Foundation held a symposium on *Pulmonary Structure and Function*, published under the editorship of de Reuck and O'Connor in 1962.

The air passages

Simplified accounts of lung function distinguish sharply between conducting air passages and areas in which gas exchange takes place. In fact, no such sharp demarcation occurs and the air passages gradually change their character showing a transition from the trachea to the alveoli, with the role of conduction gradually giving way to the role of gas exchange. *Table 1* traces the essential structural features progressively down the respiratory tract. The different levels are indicated as generations, with the trachea as the first, the main bronchi as the second, and so on down to the alveolar sacs as the twenty-third. It may be assumed that the passages of each generation bifurcate so that the number of passages in any one generation is twice that in the previous generation. In fact, there are many situations in which clear-cut bifurcation does not occur and trifurcation or lateral branching may be seen. Nevertheless, consideration of air passages in generations *as if* bifurcation occurred at each generation is very helpful and the numbers of air passages at each generation so calculated do, in fact, accord very closely with the numbers actually observed in the lungs.

Table 1 gives only the mean values for the number of generations down to each level. Thus, for example, it shows the transition from terminal bronchi to bronchioles occurring after the eleventh generation. In fact the transition may occur anywhere between the ninth and fourteenth generations.

Trachea

The trachea has a mean diameter of 1·8 cm and length of 11 cm. It is supported by U-shaped cartilages which are joined posteriorly by smooth muscle

Table 1. STRUCTURAL CHARACTERISTICS OF THE AIR PASSAGES (AFTER WEIBEL, 1963)

	Generation (mean)	*Number*	*Mean diameter (mm)*	*Area supplied*	*Cartilage*	*Muscle*	*Nutrition*	*Emplacement*	*Epithelium*
Trachea	0	1	18	Both lungs	U-shaped	Links open end of cartilage	From the bronchial circulation	Within connective tissue sheath alongside arterial vessels	Columnar ciliated
Main bronchi	1	2	13	Individual lungs					
Lobar bronchi	2 ↓ 3	4 ↓ 8	7 ↓ 5	Lobes	Irregular shaped and helical plates	Helical bands			
Segmental bronchi	4	16	4	Segments					
Small bronchi	5 ↓ 11	32 ↓ 2 000	3 ↓ 1	Secondary lobules					
Bronchioles Terminal bronchioles	12 ↓ 16	4 000 ↓ 65 000	1 ↓ 0·5		Absent	Strong helical muscle bands		Embedded directly in the lung parenchyma	Cuboidal
Respiratory bronchioles	17 ↓ 19	130 000 ↓ 500 000	0·5	Primary lobules		Muscle bands between alveoli	From the pulmonary circulation		Cuboidal to flat between the alveoli
Alveolar ducts	20 ↓ 22	1 000 000 ↓ 4 000 000	0·3	Alveoli		Thin bands in alveolar septa		Forms the lung parenchyma	Alveolar epithelium
Alveolar sacs	23	8 000 000	0·3						

bands. In spite of the cartilaginous support, the trachea is fairly easy to occlude by external pressure of the order of 5–7 kPa (50–70 cm H_2O)*. For part of its length, the trachea is not subjected to intrathoracic pressure changes but it is subject to pressures arising in the neck as, for example, due to haematoma formation after thyroidectomy. The mucosa is columnar ciliated epithelium containing numerous mucus-secreting goblet cells. The cilia beat in a co-ordinated manner causing an upward stream of mucus and foreign bodies. Cilial beat is rendered ineffective by clinical concentrations of anaesthetics (Nunn et al., 1974) and also by drying, which is very prone to occur when patients breathe dry gas through a tracheostomy.

Main, lobar and segmental bronchi (first to fourth generations)

The trachea bifurcates asymmetrically, with the right bronchus being wider than the left and leaving the long axis of the trachea at a smaller angle. It is thus more likely to receive foreign bodies, extra long endotracheal tubes, etc. Main, lobar and segmental bronchi have firm cartilaginous support in their walls, U-shaped in the main bronchi but in the form of irregular shaped and helical plates lower down. Where the cartilage is in the form of irregular plates, the bronchial muscle takes the form of helical bands which form a geodesic network extending down to the lowest limits of the air passages. The bronchial epithelium is similar to that in the trachea although the height of the cells gradually diminishes in the more peripheral passages until it becomes cuboidal in the bronchioles. Bronchi in this group are sufficiently regular in pattern to be named.

Bronchi of the first to fourth generations are subjected to the full effect of changes in intrathoracic pressure and will collapse when the intrathoracic pressure exceeds the intraluminar pressure by about 5 kPa (50 cm H_2O)*. This occurs in the larger bronchi during a forced expiration since the greater part of the alveolar-to-mouth pressure difference is taken up in the segmental bronchi under these circumstances. Therefore the intraluminar pressure within the larger bronchi remains well below the intrathoracic pressure, particularly in patients with emphysema (Macklem, Fraser and Bates, 1963; Macklem and Wilson, 1965). Collapse of the larger bronchi limits the peak expiratory flow rate in the normal subject and gives rise to the brassy note of a 'voluntary wheeze' produced in this way.

Small bronchi (fifth to eleventh generations)

The small bronchi extend through about seven generations with their diameter progressively falling from 3·5 to 1 mm. Since their number approximately doubles with each generation, the *total* cross-sectional area increases markedly with each generation to a value (at the eleventh generation) of about seven times the total cross-sectional area at the level of the lobar bronchi.

Down to the level of the smallest true bronchi, air passages lie with branches of the pulmonary artery in a sheath containing pulmonary lymphatics which

* 1 kilopascal (1 kPa) is approximately equal to 10 centimetres of water (10 cm H_2O).

may be distended by oedema fluid (*Plates 1 and 2*). They are not directly attached to the lung parenchyma and thus are not subjected to direct traction. They are nevertheless subject to intrathoracic pressure and if the extramural pressure is substantially above the intraluminar pressure, collapse will occur. It now seems likely that this does not occur to any great extent in the small bronchi since the resistance to air flow between alveoli and small bronchi is now known to be less than had formerly been deduced from study of post-mortem lungs which had been fixed without inflation. It is now believed that during a forced expiration, the intraluminar pressure in the small bronchi rapidly rises to more than 80 per cent of the alveolar pressure. This pressure is sufficient to withstand the collapsing tendency of the high extramural intrathoracic pressure.

Secondary lobule. The area of lung supplied by a small bronchus immediately before transformation to a bronchiole is sometimes referred to as a secondary lobule, each of which has a volume of about 2 ml and is defined by connective tissue septa.

Bronchioles (twelfth to sixteenth generations)

An important change occurs at about the eleventh generation where the diameter is of the order of 1 mm. Cartilage disappears from the wall of the air passages at this level, and structural rigidity ceases to be the principal factor in maintaining patency. Fortunately, at this level the air passages leave their fibrous sheath and come to be embedded directly in the lung parenchyma. Elastic recoil of the alveolar septa is then able to hold the air passags open like the guy ropes of a bell tent. The calibre of airways below the eleventh generation is, therefore, mainly influenced by lung volume, since the forces acting to hold their lumina open are stronger at high lung volume. The calibre of the bronchioles is,

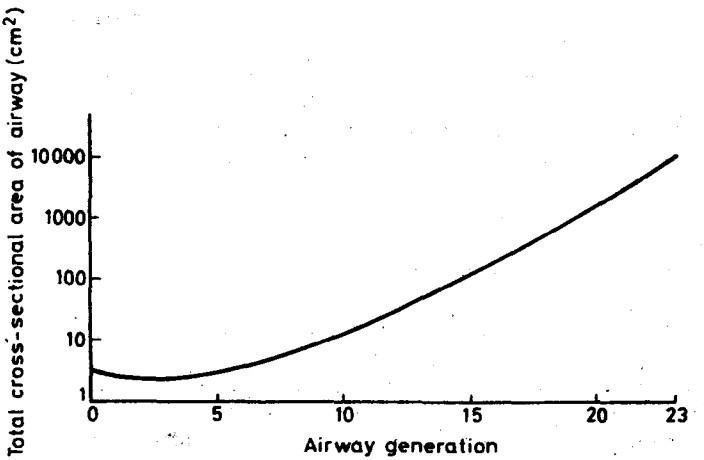

Figure 2. The total cross-sectional area of the air passages at different generations of the airways. Note that the minimal cross-sectional area is at generation 3 (lobar to segmental bronchi). The total cross-sectional area becomes very large in the smaller air passages. It approaches a square metre in the alveolar ducts. (Redrawn from data of Weibel, 1964)

however, less influenced by intrathoracic pressure than is the case in the bronchi.

In succeeding generations, the number of bronchioles increases far more rapidly than the calibre diminishes. Therefore the *total* cross-sectional area increases until, in the terminal bronchioles, it is about 30 times the area at the level of the large bronchi (*Figure 2*). It is therefore hardly surprising that the resistance to flow offered by the smaller air passages (less than 2 mm diam.) is only about one-tenth of total flow resistance (Macklem and Mead, 1967). Formerly, precisely the opposite was thought to be true, and it was believed that the major fraction of the total resistance was in the narrower vessels. This belief was in part due to earlier studies (e.g. Rohrer, 1915) which seriously underestimated the calibre of the smaller air passages. This error arose from failure to inflate the excised lung to its normal volume before fixation.

Bronchioles have strong helical muscular bands and a cuboidal epithelium. Contraction of the muscle bands is able to wrinkle the mucosa into longitudinal folds which may cause a very substantial decrease in calibre. In some studies the contraction may have been a post-mortem artefact.

Down to the terminal bronchiole the air passages derive their nutrition from the bronchial circulation and are, therefore, liable to be influenced by changes in systemic arterial blood gas levels. From this point onwards, the small air passages rely upon the pulmonary circulation for their nutrition.

Respiratory bronchioles (seventeenth to nineteenth generations)

Down to the end of the bronchioles, the function of the air passages is solely conduction and humidification. At the next generation (first order respiratory bronchiole) gas exchange occurs to a small extent and this function increases progressively through the three generations of respiratory bronchioles until, in the first order alveolar duct (twentieth generation), the entire surface is devoted to gas exchange (*Plate 3*). The respiratory bronchioles may thus be regarded as a transitional zone between bronchioles and alveolar duct with progressive changes in structure according to the change from conduction to gas exchange. The epithelium is cuboidal between the mouths of the mural alveoli but becomes progressively flatter until it finally gives way entirely to alveolar epithelium in the alveolar ducts. Like the bronchioles, the respiratory bronchioles are embedded in lung parenchyma and rely upon tissue traction for maintenance of their lumen. There is a well marked muscle layer and the muscle forms bands which loop over the opening of the alveolar ducts and the mouths of the mural alveoli. There is no significant change in the calibre of advancing generations of respiratory bronchioles and the total cross-sectional area at this level is of the order of hundreds of square centimetres.

Primary lobule or functional unit. There is some disagreement about the extent of the primary lobule. Currently the majority view is that the primary lobule is the area supplied by a first order respiratory bronchiole (*Figure 3*). According to this definition, there are about 130 000 primary lobules, each with a diameter of about 3·5 mm and containing about 2 000 alveoli (*Table 2*). They probably correspond to the areas of lung which are seen to pop open at thoracotomy during expansion of collapsed lung by inflation.