Mechanical Properties of Excised Human Lungs

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MECHANICAL PROPERTIES OF EXCISED HUMAN LUNGS

by

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I. INTRODUCTION

To date a very large body of knowledge has accumulated on both lung function and morphology. The correlation of human data collected in these separate fields is, for obvious reasons, either difficult or impossible. Although the study of the mechanical properties of excised human lungs has been popular[48,50,51,63,64], relatively few laboratories interested in lung function have combined modern physiological techniques with good morphologic studies. The purpose of the investigation reported in this thesis is to correlate some aspects of pulmonary mechanics with morphology in lungs collected at post mortem.

In particular, flow resistive and pressure-volume characteristics of normal and diseased lungs will be reported as well as the presentation of some observations on the property of air transfer between lung lobes. Prior to reviewing the pertinent literature, a discussion of the mechanical theory required to understand the physiological measurements will be presented.

II. MECHANICAL THEORY AS APPLIED TO THE LUNG

Rohrer[11,40] was perhaps the first to apply mechanical theory to the analysis of the respiratory system. However, his methods have been so elegantly developed by Mead[40] and Milic-Emili[41] that it is upon the latter work that this portion of the thesis will be based.

Newton's third law of motion states that a force applied to a body is met by an equal and opposite force developed by the body. Applying this concept to the lung, it is convenient to describe force in terms of pressure, and motion in terms of volume change. Newton's third law was restated for the lung in the following way. Any pressure applied to the lung is opposed by an equal and opposite pressure developed by the lung[40,41]. The pressure developed by the lung at any instant in time is dependent on the lung volume, flow and volume acceleration at that instant[40,41]. Furthermore, these three variables were respectively shown to represent the elasticity, frictional resistive and inertial properties of the lung[40,41]. The relationship between volume and elasticity is static while the flow resistive and acceleration inertial relationships are dynamic in quality.

1. Pressure-Volume Relationship

This relationship describes the elastic properties of the lung[40,41]. A body is said to be elastic when it returns to its initial shape after the removal of a deforming outside force, and for a perfectly elastic body the ratio of increase in length to force is constant (Hook's law).

The lung has the characteristics of an elastic body in that it returns to its initial shape after removal of a deforming pressure. However, it does not obey Hook's law and, in fact, the pressure-volume relationship exhibits a rather marked hysteresis. The factors influencing the relationship will be discussed when the appropriate literature is reviewed.

2. Pressure-Flow Relationship

This relationship describes the property of frictional resistance exhibited by the lung[40,41]. The measurement of resistance between two points requires a knowledge of the pressure difference andthe flow occurring between these points. The transpulmonary pressure or total applied force has a frictional resistance, elastic and inertial components[40,41]. The inertial component is small and it is usually ignored[12,37] but the elastic pressure must be subtracted from total pressure to get an exact measurement of the pressure required to overcome frictional resistance. This has been done by simultaneously measuring the elastic recoil pressure and subtracting it from the total pressure[40] or by observing the lung at its resonant frequency. The resonant frequency of a body is that frequency where the force required to overcome elastic and inertial forces is zero. When this condition is satisfied, the measured pressure is that required to overcome frictional resistance.

The concept of resonance is illustrated graphically in Fig. 1. Fig. 1 A shows the simultaneous relationship between volume, flow and volume acceleration which are proportional to the elastic, frictional

resistant and inertial properties of the system. This illustrates that the forces proportional to volume and volume acceleration are 180° out of phase. Fig. 1 B and 1 C show the effect of increasing frequency on these forces. The elastic forces which are proportional to volume become smaller and the inertial forces proportional to volume acceleration become larger. In Fig. 1 C, it can be seen that at a particular frequency these forces will be equal and, as they are 180° out of phase, they cancel each other leaving frictional resistance the only force to be overcome.

3. Pressure-Volume Acceleration Relationship

This relationship describes the inertial properties of the lung. Inertia is the property of matter by which it continues in a state of rest or uniform motion. The inertial force developed by the lung to oppose the applied force is dependent on a continuing motion of the lung, and is small at ordinary breathing frequencies(12,37). However, it can be seen in Fig. 1 B and 1 C that inertial forces increase with frequency and at high frequencies they become a force that must be taken into consideration.

The pertinent measurements that have been made on the lung will now be reviewed.

III. REVIEW OF THE LITERATURE

This portion of the thesis will be presented in three separate parts dealing first with lung mechanics in general, secondly with collateral air transfer and last with emphysema. Since it is impossible to review the vast literature on emphysema in a work of this nature, the literature on the morphology of emphysema, the problem of bronchitis and the theory concerning the mechanism of the increased airway resistance in emphysema will only be highlighted. Considerably more stress will be placed on the literature concerning the morphologic and mechanical measurements that have been made on emphysematous excised human lungs.

1. Mechanical Measurements Made on the Lung

A. Pressure-Volume Measurements

The earliest experiments in lung mechanics concerned the pressure-volume relationship. As early as 1820 Carson[15] attached a water manometer to the trachea of a cadaver and measured the rise in pressure when the thorax was opened. Donders repeated thse experiments in 1848[15] and noticed that inflation of the lungs caused them to recoil with greater force. Hutchinson[15], about the same time, attempted to correlate the pressure-volume relationship by inflating the lungs of two cadavers with different volumes and measuring resultant pressures. Many other investigators studied lung elasticity on either inflation[40] or on deflation[40] but it was not until both inflation and deflation were studied on the same lung that the normal hysteresis between these two limbs was discovered. This was accomplished first by McIlroy[32] in human lungs and later by Radford[53] in cat lungs. To facilitate

presentation of the static recoil properties of the lung, they will now be discussed under the headings of surface and tissue phenomena.

(a) Surface Phenomena.

Neergaard[40,54] was the first to demonstrate that forces developed at the air-tissue surface were important. He did this by measuring the marked decrease in recoil pressure when the lung was deflated after air and fluid filling from the gas-free state. Radford[53] repeated this work and after describing the pressure-volume hysteresis of the air-filled lung demonstrated the disappearance of hysteresis and markedly decreased recoil pressure when the lung was fluid filled. From these investigations both Neergaard and Radford concluded that surface forces accounted for the major proportion of the elastic recoil pressure developed by the lung.

At the same time, Pattle[47] brought forward evidence that the surface tension of the lung was less than 1 dyne per cm. Pattle obtained this evidence in part from squeezing the cut surface of the lung under water and obtaining stable bubbles. He concluded that the stability of these bubbles was due to a true surface film which exerted a surface pressure almost equal to the surface tension of the liquid in which it was immersed. Since blood never forms bubbles and tracheal mucus did not appear to contain the stabilizing substance, he postulated that it arose from the depths of the lung.

These two investigations resulted in controversy. Neergaard and Radford, on the one hand, stated that surface forces were responsible for the major portion of lung retractive force, and Pattle who stated that the surface tension of the lung was very

small. Brown[4,5] and Clements[8,9] resolved this difficulty by demonstrating that the lung surface exhibits marked area tension hysteresis. That is, the surface forces which develop while the lung surface is expanding (during inflation) are much greater than those which develop while the lung surface is contracting (during deflation).

A review of the literature concerning surfactant, the remarkable substance responsible for the area tension hysteresis, and the closely related problem of airway stability is beyond the scope of this work.

(b) Tissue Forces

(i) Connective Tissue. Collagen, elastin and reticulin fibres appear to be responsible for a large portion of the lung tissue elasticity[40]. Elastic fibres (i.e. fibres made of elastin) can be easily stretched by seventy per cent of their resting length[40]. By contrast, collagen and reticular fibres are highly elastic and required large forces for a very small change in length[40].

Setnikar[40] proposed a model for the behaviour of elastic and collagenous fibres in lungs similar to that suggested by Burton[6] for these fibres in blood vessels. Mead[40] has modified this equation so that it predicts the observed behaviour of lung tissue quite well. Pierce[49] demonstrated a complete loss of retractive force in saline-filled lungs treated with elastase to dissolve elastic fibres. This observation suggests that elastic fibres are responsible for retraction and that collagen acts as a supporting framework. Radford thought this probably represented an oversimplification[54] and suggested that

there was an interaction between collagen and elastin. However, there is little information from which to deduce what this interaction might be.

(ii) Smooth Muscle. Although the morphology of smooth muscle has been extensively studied[29], its exact function is unknown. Estimates of the importance of smooth muscle to tissue recoil pressure have varied. Radford and Lefcoe[52] concluded that it made no contribution after a study of excised dog lung maximally stimulated with acetyl choline in Locke-Ringer's solution. Nadel et al.[44], on the other hand, found that when the peripheral musculature was stimulated by injecting barium sulphate, microemboli and histamine into the pulmonary artery of living dogs, a moderate effect on lung compliance was observed. More recent investigations by Woolcock and Macklem tend to confirm this result[62].

(iii) Vasculature. The contribution of pulmonary vasculature to lung retraction is unknown. However, there has been a great deal of work on the effect of vascular engorgement[54]. Many of these investigations are difficult to interpret as it is impossible to separate the effect of the vascular volume per se and the well known changes that engorgement produces in the lung tissue. This is particularly true of chronic engorgement (.e.g mitral stenosis) where structural changes are well known[46].

(iv) Epithelial Tissue of Bronchi and Alveoli. Radford[54] has shown that the pressure-volume curves of excised lungs is unchanged after several days of storage under refrigerated conditions. Since it is well known that this treatment has an adverse effect of these delicate tissues, it is unlikely that they contribute to elastic recoil.

In summary, the pressure-volume relationship describes the elastic properties of the lung. Surface phenomena account for a large proportion of the recoil pressure and the majority of the difference in pressure between inflation and deflation limbs of the pressure volume curve. The contribution of the various components of lung tissue to recoil pressure have not been clearly worked out. Connective tissue appears to play the most important role by the contribution of various components of this tissue is not altogether clear.

The possibility of regional differences in static pressure-volume characteristics of the lung will undoubtedly be a fruitful area of research. Otis et al.[45] have shown that the distribution of ventilation in the lung is independent of breathing frequency. It follows that ventilation distribution must then be dependent on static lung properties. Milic-Emili[43] has recently suggested that ventilation distribution is dependent on regional differences in transpulmonary pressure but he points out that relatively few studies have investigated the pressure-volume relationship of lung regions. Frank[16] and later Faridy and Milic-Emili[14] have demonstrated small but significant differences in the pressure-volume characteristics of the upper and lower lobes of dog lungs. A preliminary investigation comparing lobes of human lungs has been included in this study.

B. Pressure-Flow Measurements made on the Lung

As previously stated, this relationship describes the frictional resistance offered by the lung. To facilitate discussion, the methods for measuring total resistance will be presented first, followed by the methods for measuring the resistance of portions of the lung.

(a) Total Pulmonary Resistance

In the discussion of mechanical theory, it was pointed out that this measurement required a knowledge of the resistive component of total pressure and the flow which this pressure produced. In two of the three methods to be described, the inertial pressures are ignored and the elastic pressures are subtracted from the total pressure to provide the flow resistive component of pressure. The pressure applied to the lung and those developed by the lung in opposition to the applied pressure are summarized in equation -

$$P_L = P_{el} + P_{res} + P_{in} \qquad (1)$$

where P_L = applied pressure and P_{el}, P_{res} and P_{in} are the elastic, resistive and inertial components of the pressure developed by the lung. Ignoring inertial pressure for reasons outlined in Chapter II (3) and solving for P_{res}

$$P_{res} = P_L - P_{el} \qquad (2)$$

The first separation of the elastic and resistive components of total pressure was accomplished by Neergaard and Wirz[11]. They pointed out that at two points in the respiratory cycle the flow was zero and the pressure at these points represented elastic forces only. Thus at end expiration

$$P_{el} = P_o \qquad (3)$$

and at end inspiration

$$P_{el} = P_o + \frac{1}{C_{dyne}} \Delta V \qquad (4)$$

where C_{dyne} = the dynamic compliance, or ratio of tidal volume to the change in pressure between the points of zero flow at the extremes of tidal volume. Po is the initial pressure and ΔV the volume change.

Substituting (4) in (2) we obtain

$$P_{res} = P_L - (P_o + \frac{1}{C_{dyne}} \Delta V) \qquad (5)$$

This equation can be solved in a variety of ways[40]. Mead and Whittenberger's technique for subtracting elastic recoil pressure from total pressure electrically is perhaps the most elegant[36].

The second method of separating flow resistive pressure was introduced by Vuelleumier[40] but has been most extensively applied by Fry[17]. They found that if the airway was suddenly closed, the pressure between the airway and the pleural surface changed abruptly by and amount equal to the flow resistive pressure.

Before interruption

$$P_L(1) = P_{el} + P_{res}$$

After interruption

$$P_L(2) = P_{el}$$

and $P_{res} = P_L(1) - P_L(2)$.

A third method for measuring the resistive component of total pressure was introduced by Mead[39]. He placed a loudspeaker in a pressurized box and connected it to a lung. By blowing air into the box and allowing it to leak through the speaker cones he was able to inflate the lung to any desired pressure. He then activated the speaker with a sine wave generator to blow air into and out of the lungs. By oscillating the lung at its resonant frequency (see Chapter II (2)) he was able to measure the flow resistive pressure directly. In all three cases, the division of the obtained resistive pressure by flow measured simultaneously provided the total pulmonary resistance.

(b) Measurements of Components of Pulmonary Resistance

(i) Separation of Total Resistance into Gas and Tissue Components. Rohrer[11] thought that the direct measurement of the gas flow resistance to be such a formidable problem that he made estimates of flow resistance by applying aerodynamic principles with anatomic measurements obtained at post mortem. These estimates were handicapped by lack of precise anatomical knowledge and the fact that the principles of flow through a highly branched distendable system are poorly understood even to-day[40]. However, they were surprisingly accurate for predicting the resistance of some portions of the airway[40]. Measurement of gas flow resistance is dependent on simultaneous knowledge of the pressure change from trachea to alveolus and the flow that is produced by this pressure change. The most successful method has been the indirect measurement of alveolar pressure by measuring alveolar gas compression and expansion. This was first proposed and attempted by Sonne[40] but its first successful application was by Dubois et al.[10].

Dubois estimated alveolar pressure by placing his subjects in a body plethysmograph and instructing them to breathe through a pneumotachograph. Since the system was completely enclosed, the volume of gas in the lungs and plethysmograph was constant. If there was no airway resistance, the alveolar pressure would be equal to the plethysmograph pressure throughout the respiratory cycle. However, the alveolar pressure must have been less than box pressure during inspiration and greater than box pressure during expiration to make gas flow through the airways. Since the amount of gas in plethysmograph and lung was constant, the pressure changes in the plethysmograph were opposite in

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sign to the pressure changes in the alveolus during the breathing cycle. After his subjects had panted through the pneumotachograph, Dubois then calibrated the fluctuations in chamber pressure in terms of alveolar pressure by closing off the airway and having the subject continue to pant. With flow stopped, airway pressure was equal to alveolar pressure. The relationship between alveolar pressure and chamber pressure established by this manouvre could then be applied to measurements made prior to airway closure. In this way the box pressure changes reflecting alveolar gas expansion and contraction were separated from box pressure changes reflecting alveolar pressure required to produce flow.

Other attempts to measure alveolar pressure have been less successful. For example, Neergaard and Wirz[40] thought that they could measure alveolar pressure with an interrupter. They reasoned that because the alveolar gas volume was large in relation to airway volume that after interruption the alveolar pressure would rapidly equilibrate with mouth pressure. This has been shown to be an incorrect assumption[42].

Another approach to separating total resistance into gas and tissue components has been the measurement of the tissue frictional resistance. Bayliss and Robertson[2] were the first to attempt this but the most sophisticated study was done by McIlroy[34]. The principle involves measurement of total pulmonary resistance using gases with different viscosity. The resistance at zero viscosity, found by extrapolation, was attributed to the lung tissue. McIlroy's study was the best of this type in that he used gas mixtures that took gas density into account and insured a similar distribution of turbulence in the

airways with each determination. By subtracting lung tissue resistance from total resistance the resistance to gas flow could be calculated.

(ii) Resistance of the Lower Airways. The contribution of various portions of the lower airway to the total resistance has until recently never been measured. The problem was that there was no way of measuring pressure in the small airways. Macklem and Mead[28] solved this problem by an ingenious method of measuring these pressures. They did this by introducing a piano wire into the trachea and pushing it down the airway until it cut through a bronchial wall, the parenchyma and pleural surface. They then attached a small piece of polyethylene tubing on the tracheal end of the piano wire and pulled on the pleural end so that the tubing was dragged into the tracheobronchial tree in a retrograde fashion. A bell, 3 mm. in diameter, was placed on the tip of this tubing so that it would wedge in a small bronchus. By measuring the pressure drop from the retrograde catheter to the pleural surface the resistance of the airways peripheral to the catheter was found. Simultaneous measurement of total resistance allowed the resistance of the airways central to the catheter to be found by subtraction. Macklem used Mead's oscillation technique[39] to measure total resistance and the technique of electrically subtracting elastic recoil pressures of Mead and Whittenberger[36] to measure the resistance of the peripheral airways. These experiments carried out in dogs showed that the bulk of the resistance was in the airways which were greater than 2 mm. in diameter. These measurements represent an important advance and the technique used to obtain them has been applied in this study to obtain similar measurements on human lungs.

(iii) Resistance of Lung Tissue. The frictional resistance offered by lung tissue can be calculated by measuring the resistance from trachea to alveolus and subtracting this value from the total resistance. When Marshall and Dubois[30] did this using his technique for measuring alveolar pressure, he found that the lung tissue accounted for about 20% of the total frictional resistance. McIlroy[34] estimated that it was about twice this amount using his method of varying gas viscosity. Macklem's data[28] suggest that both of these estimates are too high in that the resistance of the peripheral airways and lung tissue provided only 10% of the total resistance. The distance between the trachea and the wedged catheter which contains no tissue component provided the greatest amount of resistance in their study. Mead[40] postulated that some of the difference between the data of McIlroy and Dubois might be the breathing frequency at which the measurements were made. However, it is unlikely that the question of the tissues' contribution to pulmonary frictional resistance will be settled until a completely satisfactory method of measuring alveolar pressure at all respiratory frequencies is found.

2. Inter-Alveolar Communication and Collateral Air Transfer

A. Inter-Alveolar Communications

Inter-alveolar communications have been discussed in the literature vigorously and for a long time. Review of early studies can be found dating from Williams (1859). The sides of the argument in this early literature are described by Loosli[27] made up by Reisseissen and Rossignol who maintained that the alveoli ended in

blind sacs and Rainy, Henle and Delafield who thought they saw small communications between terminal alveoli.

Kohn aroused new interest in the subject in 1893 when he described strands of fibrin passing between alveoli in lungs with acute fibrinous pneumonia. Hauser in the same year published a similar description and referred to these communications as "pores of Kohn".

The literature then becomes a confusing series of charge and countercharge well outlined by Loosli[27] until the final establishment by a number of investigators that these communications could be demonstrated if thick well-stained sections were made of lungs fixed in inflation. Loosli concluded, after his excellent review of the subject, that "the pores are normal constituents of the alveolar walls in the lungs of a wide variety of mammals including man". These pores are not formed by inflammatory process but are only more frequently noted on thin sections of lungs with pathology (especially fibrinous pneumonia) where they contain fibrin and cells.

B. Channels of Communication Arising from Bronchioles

Much more recently (1955) Lambert[24] described communications between bronchioles and alveoli in human lungs in which the trachea had been clamped prior to their removal. Serial drawings revealed that when these canals originated from respiratory bronchioles they connected to alveolar sacs at the tips of alveolar ducts supplied by the parent bronchiole. However, when they arose from terminal bronchioles, they sometimes connected to alveoli supplied by other bronchiolar systems.

The most recent data on channels of collateral ventilation were supplied by Martin[31] who demonstrated connections between respiratory bronchioles of the dog.

C. Studies of Air Transfer Through Collateral Channels

The first significant study of transfer of air between lung lobules* was undertaken by Van Allen and Lindskog[59]. They demonstrated the passage of air between "lobules" (but not lobes) of excised dog, rabbit and human lungs. They also demonstrated that this collateral ventilation could occur in a spontaneously breathing animal. This was done by introducing a dilatable cannula into a bronchus and isolating it from the rest of the bronchial tree. The cannula was connected to a tube which was placed under water so that only expiration could occur. They observed that during inspiration water was sucked up the tube about 5 centimetres but during expiration air freely bubbled from the cannula. During a period of one half hour air far in excess of the volume of the cannulated "lobule" was collected and could only have been obtained from adjacent "lobules". Baarsma et al.[1] confirmed that collateral ventilation occurred in man by inflating the cuff of a rubber cannula beyond the apical bronchus of the lower lobe thus isolating the basal from the apical segment. By connecting the catheter to a spirometer they were able to measure the amount of air which reached the basal segments of the lower lobe from the apical segments. The main interest of these

*Van Allen used the term lobule rather loosely and it is likely he was referring to a lobar segment or sub segment.

authors was the mechanism of atelectasis. Their conclusion in essence was that atelectasis of a portion of the lung occurred when its bronchus was occluded only if the collateral channels were also blocked. Collateral ventilation across incomplete labor fissures has attracted less attention than ventilation across lung segments. Van Allen studied the phenomenon but stated that it occurred only when the lobule he inflated was distended beyond the normal. Kent and Blades[23], after a careful study of 227 lungs, stated that a truly complete lobar fissure was rare in human lungs. A re-investigation into this interesting phenomenon appeared to be warranted as no study on the effect of disease on the channels in lobar fissures could be found. The degree of collateral ventilation across lobar fissures in emphysema is of special interest as the inter-alveolar fenestrae[3] which occur in this condition are abnormal openings which should transmit a larger volume of air than the pores of Kohn seen in normal lungs.

3. Morphologic Aspects of Emphysema and Bronchitis

A. Introduction

The first description of emphysema was attributed to Laennec[58]. Although he and several other 19th century investigators[58] stressed the macroscopic appearance of the disease, the introduction of the microscope to the study of the lung reduced the pathologic diagnosis of emphysema to a microscopic description. The majority of these observations were made from a small sample of any given lung which had usually been fixed in an uninflated state[58]. It is not surprising that this data was of little help to those attempting to apply techniques of physiology to

the study of disease. The field of clinical pulmonary physiology rapidly advanced in the first half of this century under the now great names of Baldwin, Cournand, Christie and Comroe. Their studies provided a stimulus for a re-investigation into the morphology of the lung and its diseases, which has been led by the Cardiff group in Wales, McLean in Australia, Wyatt and Thurlbeck in North America, Weibel, Dunnill, Heard and many other that they have stimulated. These investigators have applied techniques to lung morphology often more familiar to statisticians and geologists than biologists. These techniques allowed lung morphology and pathology to be discribed in a quantitative sense. This portion of the vast literature on emphysema is very important to a study of lung structure and function but, prior to presenting it review, emphysema will be defined.

B. Definition of Emphysema

Two definitions of emphysema are avilable. A Ciba Guest Symposium[7] decided that the term emphysema should be applied to a condition of the lung characterized by an increase beyond the normal in the size of the airspaces distal to the terminal bronchiole either from dilatation or destruction of their walls. Both the American Thoracic Society and the World Health Organization have limited the use of the term to enlargement of these airspaces accompanied by destruction. The important advantages of a definition requiring destruction are that destruction is more easily recognized than overinflation and it is responsible for the clinical syndrome of emphysema. The point concerning ease of recognition is very important. Knowledge concerning the precise size of the airspaces

is incomplete and therefore recognition of overinflation is difficult. This fact results from the technical difficulties arising in the histological study of the lung where the degree of inflation during fixation, amount of tissue shrinkage and many other factors must be controlled. Studies of lung morphology when all these variables are taken into account have only begun. The disadvantages of a definition requiring destruction are that it does away with well known term such as compensatory emphysema, and that it does not define destruction. For example, the aging lung shows an increase in size of airspaces together with an increase in size of the alveolar pores and it is not clear whether this should be described as senile emphysema or senile overinflation.

C. Types of Emphysema.

A significant milestone in the more recent literature on emphysema was the description of two fundamentally different types by Gough[18] and the amplification of this concept five years later with Leopold[26]. Although many forms of emphysema have been described[58], this discussion will be limited to the centrilobular and panlobular types described by these investigators because the cases to be presented represent a mixture of these two forms.

(a) Centrilobular Emphysema

The lobule, i.e. secondary lobule of Miller, is the smallest discrete portion of the lung surrounded by a lobular septum and thus is a unit of varying size. Centrilobular emphysema is primarily a destructive lesion occurring in the region of the respiratory bronchioles[26]. The destroyed and enlarged respiratory bronchioles

tend to become confluent and form spaces situated in the centre of the lobules. These lesions occur more frequently and more severely in the upper zones of the lung[57]. The supplying bronchioles are narrowed in 60% of cases[26] but are always patent[50]. Inflammation of the supplying bronchioles in particular and the distal bronchioles in general is always found[26].

(b) Panlobular Emphysema

In this condition, the entire acinus (that part of the lung distal to the terminal bronchiole) is involved. The involvement of every portion of the acinus can only be demonstrated by serial sectioning. Since this is impractical, the term is generally applied to a characteristic morphologic appearance. Thurlbeck[58] suggests that the term panlobular emphysema should not be applied to centrilobular emphysema that has expanded to involve the entire lobule and points out that these cases can usually be recognized by the presence of severe centrilobular emphysema in adjacent areas.

Panlobular emphysema is more or less random in its position in the lung in consecutive cases, although there is a tendency for more frequent occurrence in the anterior basal segment and the tip of the lingula[57]. The mean age of patients with panlobular emphysema is older than that of those with centrilobular emphysema. This type of emphysema is more common in men but in women it occurs more frequently than does centrilobular emphysema. Most observers[58] agree with Gough's contension that they are two fundamentally different forms of emphysema but their frequent coexistence suggests one or more common pathologic factors.

D. Chronic Bronchitis

It is impossible to discuss emphysema without including the associated problem of bronchitis. Laennec[58] was the first to implicate bronchial lesions in emphysema and since his time it has been a variable that is difficult to assess. The definition of chronic bronchitis depends on whether the problem is approached from a clinical or a morphologic point of view. Morphologic recognition depends on the demonstration of hypertrophy of the mucus-secreting elements of the tracheobronchial tree, while the clinical diagnosis is based on a history of chronic productive cough. Demonstration of mucus gland hypertrophy has rested on the Reid index or ratio of mucus gland to wall thickness. This criterion is not completely satisfactory as it entirely avoids the important problem of measuring the goblet cell secretions and mucus secretion found in small airways. The introduction of bronchography has helped in the appreciation of small airway disease and in the hands of Reid, Leopold and others[25] criteria for the recognition of small airway plugging and inflammatory narrowing have been worked out. Measurement of the degree of airway obstruction due to mucus plugging, inflammatory narrowing and the associated problem of loss of peribronchiolar alveolar support quantitatively is another matter and the surface of this complex problem has barely been scratched.

E. Airway Resistance as a Factor in the Etiology of Emphysema

The discussion of the cause of pulmonary emphysema is at once both easy and extremely difficult. It is easy because it can be confidently stated that the etiology of this disorder is unknown. It is

D. Chronic Bronchitis

It is impossible to discuss emphysema without including the associated problem of bronchitis. Laennec[58] was the first to implicate bronchial lesions in emphysema and since his time it has been a variable that is difficult to assess. The definition of chronic bronchitis depends on whether the problem is approached from a clinical or a morphologic point of view. Morphologic recognition depends on the demonstration of hypertrophy of the mucus-secreting elements of the tracheobronchial tree, while the clinical diagnosis is based on a history of chronic productive cough. Demonstration of mucus gland hypertrophy has rested on the Reid index or ratio of mucus gland to wall thickness. This criterion is not completely satisfactory as it entirely avoids the important problem of measuring the goblet cell secretions and mucus secretion found in small airways. The introduction of bronchography has helped in the appreciation of small airway disease and in the hands of Reid, Leopold and others[25] criteria for the recognition of small airway plugging and inflammatory narrowing have been worked out. Measurement of the degree of airway obstruction due to mucus plugging, inflammatory narrowing and the associated problem of loss of peribronchiolar alveolar support quantitatively is another matter and the surface of this complex problem has barely been scratched.

E. Airway Resistance as a Factor in the Etiology of Emphysema

The discussion of the cause of pulmonary emphysema is at once both easy and extremely difficult. It is easy because it can be confidently stated that the etiology of this disorder is unknown. It is

difficult in that so many different factors are presumably important. An important fact is that emphysema is nearly always associated with airway obstruction, but the site and mechanism of this obstruction are controversial. Leopold and Gough[26] in their description of centrilobular emphysema postulated that the obstruction was functional due to removal of peribronchiolar alveolar support by the disease process. McLean[35], on the other hand, stressed the importance of bronchiolar mucus plugging, inflammatory narrowing and obliteration. He felt that if a bronchiole was obstructed with a plug the airspaces beyond would be collaterally ventilated and that under normal circumstances the mucus plugs would be removed during a cough. If the bronchiole were partially or completely obliterated, he theorized that the trapping of collaterally ventilated air would lead to breakdown of alveolar walls. This theory was criticized because he was unable to demonstrate obliteration of small airways. This is not surprising if one reflects on the difficulty of the problem he faced. First, there are tens of thousands of these small airways which must be examined and second, a histological section of any one of them is thin enough to miss an obstruction a short distance away. The importance of collapse of the larger airways has been stressed by many investigators[58] but relative importance of peripheral to central obstruction has been difficult to assess because a method has not been available to measure the resistance of various portions of the airway. The introduction of a technique for accomplishing this task by Macklem and Mead[28] has provided a method for partitioning lower airway resistance and the first measurements obtained in emphysematous human lungs using this technique will be presented in this study.

F. Measurement of Emphysema

Chayes[13] has said in the preface of a book dealing with the methods available to those interested in the quantitative composition of rocks that his object was to put "numerical flesh on the bones of definition". Attempts to accomplish this in normal and diseased lungs have been relatively recent[13] and the problems involved are worthy of review.

The procedures of fixation, dehydration, clearing and embedding all alter the dimensions of an organ and thus careful measurements are needed to determine both volume of the fixed organ, and the size of the fixed histological section, so that processing constants can be determined. The initial problem in a study of this type is a method of fixing the lung. The available methods have been reviewed by Heard[20] and they usually involve some form of infusion of fixative into the trachea. Hartung[19] pointed out that fixation under high pressure is unsuitable for quantitative study and many investigators have switched to a method of formalin fume fixation described by Weibel and Vidone[60]. Heard's method[20] of fixation at a constant pressure of formalin is a satisfactory alternative and was in fact the method used in the present study. Lung volume is usually assessed by water displacement and fixation constants for the conversion of fixed to fresh lung can be calculated by measuring fresh and fixed volume. The quantitation of either normal or diseased structures in a given volume of lung is in a sense a geological problem. In 1848, Delesse[61] put forward a principle which stated that in a section of a sample of rock the proportion of surface area taken up by a particular mineral was similar to the

volume of that mineral in the entire sample. This principle has been most extensively applied to the lung by Weibel[61] who pioneered the quantitation of lung morphology. Dunnill[13] was the first to apply this technique to the quantitation of emphysema. He estimated surface involvement by placing a specially prepared grid at random over the cut surface of a lung. He assessed the surface of slices of the lung with a hand lens through spots drawn on the grid. The number of spots involved by emphysema was expressed as a percentage of total spots examined. The Delesse's principle allowed conversion of this area relationship to the proportion of emphysema in the total volume of lung. A modification of this technique has been introduced by Thurlbeck[56] using a dissecting microscope to assess the lung surface through the holes in a similar grid.

As emphysema destroys lung parenchyma, an assessment of the internal surface area of the lung would seem a reasonable approach to quantitating the disease. Tomkeieff[13] was the first to draw attention to a method of finding the surface area of small objects from their area of projection. This method was employed by Duguid et al.[13] to calculate the respiratory surface area of the lung in experimental animals. Weibel and Gomez[61] have dealt with the mathematical development of the formula for internal surface area and the practical considerations in calculating the mean linear intercept (Lm) required for its solution. Discussion of these factors is beyond the scope of this work and will not be presented.

Unfortunately, both point-counting and estimates of internal surface area have serious drawbacks in assessing emphysema. The point-

counting method estimates the extent of emphysema accurately but it is impossible to assess severity. Internal surface area estimates have recently been shown by Thurlbeck[56] to be well within the normal range in mild emphysema. This is particularly true if the emphysema is centrilobular in type. This situation has caused some pathologists to revert to the more subjective methods. Thurlbeck[55] has recently circulated a series of Gough sections to a number of expert pathologists and asked them to independently score the extent and severity of the emphysema present. The combined score for each case was then calculated and various subjective and objective methods of measuring emphysema were compared to this combined score. Thurlbeck[55] has suggested that the circulation of these sections to other pathologists to allow them to compare their estimates of emphysema to the experts may provide a method of imposing a degree of order on this confusing field.

G. Mechanical Properties of Excised Emphysematous Human Lungs

A review of the literature on the lung mechanical properties in general has been presented and this portion of the discussion will deal with lung mechanics in disease. For the purpose of continuity these measurements will be discussed under headings similar to those in the general review.

(a) Pressure-Volume Characteristics

The study of this relationship is difficult in emphysematous lungs because of the difficulty in obtaining a lung with emphysema in a leak-free state. Perhaps for this reason no study separating tissue and surface forces in emphysema could be found. Milestones in the more recent literature were the investigations of McIlroy and

Christie[33]. These investigators felt that the loss of elasticity in emphysema might be due to an increase in the viscous properties of the lung in this condition. However, their measurement of viscous resistance of lungs was arbitrary and makes their results difficult to interpret. Pratt[51] has extensively studied inflation curves of emphysematous lungs and found that they were "excessively compliant" but, since he does not show the deflation curve, it is difficult to assess the amount of leakage that occurred. Wright[63] has developed a preservative solution to aid in obtaining a clean specimen with a reduced number of artifacts. However, this solution destroys surfactant and thus introduces an artifact of its own.

(b) Pressure-Flow Characteristics

A significant starting point in the study of frictional resistance in excised emphysematous lungs was again found in the work of McIlroy and Christie[33]. They reported that the observed increase in resistance in emphysema was due to changes in the lung rather than airway obstruction. The problems involved in measuring lung tissue resistance are referred to in Chapter III Section B (b) (iii) of this thesis and it is likely that this investigation was hampered by the difficulties inherent in their method. However, this in no way detracts from the fact that they initiated new interest in the properties of excised lungs.

Wyatt[64] reported an increase in lung resistance with severity of emphysema but failed to take elastic recoil pressure into account. Unfortunately, most other investigators have chosen clinical tools for measuring airway resistance. Although examination of

expiratory flow rates in living patients are well established measurements, their application to the measurement of resistance in excised lungs is not clear. Since the excised lung affords an excellent opportunity of measuring resistance directly, it is a pity that so much effort has been invested in examining its reflection by measuring flow rates alone. The investigations led by Pratt[50] and Petty[48] are good examples of this type of study and, while they are of interest in themselves, they fail to provide hard data of a type that might lead to a better understanding of airway resistance in lungs with emphysema and bronchitis.

IV. METHODS

All lungs were collected from the autopsy service of the Royal Victoria Hospital.

1. Physiologic Measurements

A. Pressure-Volume Studies

Deflation limbs of the pressure-volume diagram of upper and lower lobes from seven lungs were compared, using the apparatus shown in Fig. 2. A cannula with a side opening hole was tied into the trachea and the lung not under study was clamped off. A catheter with an inflatable rubber tip (Foley catheter) was inserted through the side opening in the cannula and introduced into the desired lobar bronchus. That bronchus was then carefully dissected and the inflated rubber tip was tied in place. Volume change was measured with an Emerson excised lung plethysmograph. Lobar distending pressure was measured by comparing the pressure inside the plethysmograph to the pressure in the lobar airway obtained from a small polyethylene tube inserted through the rubber catheter on a Sanborn series 267 B transducer. Air that was transferred across the lobar fissure was allowed free access to the outside of the plethysmograph through the cannula so that the lobe not under study would not inflate. The pressure and volume signals were recorded on both a Sanborn 4-channel recorder and a tektronix storage oscilloscope.

B. Air Transfer Across Lobar Fissure

This data was collected using the apparatus shown in Fig. 3. The arrangement of the metal cannula and Foley catheter were described

in section (A) as were the methods for measuring lobar distending pressure and volume. In these experiments flow from the collaterally ventilated lobe was measured at the trachea using a pneumotachograph and Sanborn series 270 differential pressure transducer. The pressure drop across the lobar fissure was measured by inserting catheters with a bell 3 mm. in diameter beneath the pleural surface in each lobe close to the major fissure. The pressure difference between these catheters was measured with a Sanborn series 267 B transducer. The pressure drop along the airways of the lobe into which flow occurred was measured by comparing lobar catheter pressure and tracheal pressure on a similar transducer. The resistance across the lobar fissure and out of the lobe receiving transferred air was calculated by dividing these pressure differences by flow measured under steady state conditions. The pressure, volume and flow signals were recorded on both a 4-channel Sanborn recorder and a tektronic storage oscilloscope. Dual trace X and Y axes on this oscilloscope allowed simultaneous comparison of the pressure volume and collateral flow volume relationships.

Collateral air transfer was measured from the lower to the upper lobe of one lung from eight normal and eight emphysematous cases. The interrelationship of lobar distending pressure, lobar volume and collateral flow out of the lobe was explored in three of the normal cases. The opening pressure of upper lobes when filled via the lobar bronchus was compared to their opening pressures when filled from the lower lobe via the lobar fissure in three of the emphysematous cases. Resistance across the lobar fissure and resistance out of the lobe

receiving collateral air drift was compared in three of the normal and three of the emphysematous cases.

C. Pulmonary Resistance Studies

The technique for partitioning pulmonary resistance developed by Macklem and Mead[28] was used in this portion of the study. The lungs from nine cases were collected and studied. Four of these cases died suddenly and had no anatomic evidence of bronchitis or emphysema. Of the remaining five, four had chronic bronchitis and emphysema and one had widespread varicose bronchiectasis.

The catheter was placed in the lung to be studied by introducing a stiff polyethylene tube 3 mm. in diameter into the bronchial tree until it wedged. A piano wire was then pushed through this tube until it cut through the bronchial wall parenchyma and pleural surface. The tube was then removed leaving the piano wire extending from trachea to pleural surface. A smaller polyethylene catheter 1.2 mm. in internal diameter was attached to the piano wire at the trachea. By pulling on the piano wire at the pleural surface, the catheter was pulled into the bronchial tree and out through the pleura until a 3 mm. bell at its tip was wedged in a small bronchus. The piano wire on the other end of the catheter was then removed. A fine silk thread placed around the catheter bell was used to allow the catheter to be cleared when it became blocked and to allow it to be easily found during dissection of the bronchial tree.

Resistance measurements were made using the apparatus shown in Fig. 4. The lung was placed in a plethysmograph and connected to a loudspeaker placed in a pressurized box. It was then inflated to a

pressure of 25 to 30 cm. of water by blowing air into the box and allowing it to leak through the speaker cones into the lung. At various distending pressures the deflation was stopped and air was blown into and out of the lung in a sine wave pattern at a frequency of four cycles per second. This was done by activating the loudspeaker with a sine wave generator. Flow was measured with a pneumotachograph at the trachea. The resistance central to the catheter tip Rc was calculated by electrically subtracting inertial pressure from the total pressure drop from trachea to catheter tip and dividing the remainder by flow. The resistance peripheral to the catheter tip Rp was calculated by electrically subtracting elastic pressure from the total pressure drop from the catheter tip to the pleural surface and dividing the remainder by flow. The total resistance was calculated by adding Rp and Rc. Resistance was partitioned in this manner with the catheter tip in various positions from the tracheal carina to the wedge position.

The pressure differences between the trachea and catheter and those between the catheter and pleural surface were measured on Sanborn 268 B pressure transducers. The pressure flow relationships of the airways central and peripheral to the catheter tip were displayed separately on two oscilloscopes. The electrical subtractions were accomplished by the method of Mead and Whittenberger[36] and the flow resistant component of the total pressure in each case along with flow were recorded on a Sanborn 4-channel recorder. Resistance was then calculated from these records.

D. Morphologic Studies

After completion of all physiologic studies, the morphologic studies were begun. A bronchogram was performed in each case using finely particulate lead[25]. X-ray films were taken at distending pressures of 20, 10, 5 and 0 cm. of water distending pressure after the lungs had first been fully inflated. The position of catheters from studies (B) and (C) were marked by filling them with radio-opaque oil. The lungs were then fixed at a constant pressure of 25 cm. of formalin[20]. After at least 18 hours of fixation, the position of the bronchial catheters was determined by dissecting the bronchial tree to the wedged position. In practice this was easily accomplished when the dissection followed the thread placed around the catheter tip. The position of subpleural catheters was determined by removing them in a block of tissue. This block was then cut so that the scalpel passed directly in front of the catheter tip and both cut surfaces were examined under water using a dissecting microscope. Histologic sections were taken at all catheter sites. The lungs were then sliced saggitally and emphysema was identified on barium sulphate impregnated slices[21]. A subjective grading system[57] and stratified random point count[13] were used to measure emphysema. Stratified random blocks of tissue were taken for histological examination and bronchial sections for the measurement of the Reid index.

V. RESULTS

1. Pressure-Volume Studies

Table I shows the pressure-volume data obtained from the upper and lower lobes of seven lungs. Volume is expressed as a per cent of lobar vital capacity and pressure in centimetres of water. The mean deflation pressure volume curves from the upper and lower lobes of these seven lungs are compared in Fig. 5 which illustrates that there is no statistically significant difference between the upper and lower lobes.

2. Air Transfer Studies

The collateral air transfer from lower to upper lobes is shown in Table II. The effects of pressure and volume of a lobe on collateral air drift out of it are illustrated in Fig. 6. A comparison of lobar opening pressures via the lobar bronchus and collateral channels in an incomplete fissure for three emphysematous upper lobes is shown in Table III. The resistance across the lobar fissure, compared to the resistance out of a lobe receiving air across the fissure in eight cases, is shown in Table IV.

3. Pulmonary Resistance Studies

In all cases the retrograde catheter was wedged in a small bronchus about 2-3 mm. in diameter from the fifth to the thirteenth generation (lobar = 1). The results of nine catheters from four normal cases are shown in Fig. 11 and illustrate the relationship between distending pressure and resistance. The resistance of the peripheral airways is small in comparison to total resistance and

varies with trans pulmonary pressure in a similar way. A whole lung section and the results of two catheters from a representative normal case are shown in Fig. 12. This illustrates that the total resistance is the same no matter where the catheter is placed but the peripheral resistance becomes smaller as the catheter is placed farther out. A whole lung section and the results of a retrograde catheter from a case of emphysema and bronchitis are shown in Fig. 13. The increase in resistance is shown to be due to a large increase in the resistance peripheral to the catheter. Fig. 14 shows a whole lung section and results from the catheter from a case of severe varicose bronchiectasis. A bronchogram done on this case is shown in Fig. 15. Here again the markedly increased resistance was due to an increase in the resistance peripheral to the catheter tip.

Table V shows a comparison of representative catheter studies from all cases. The comparison was made at a distending pressure of 5 cm. H_2O with the catheter placed in roughly comparable positions in the tracheobronchial tree. The total resistance in the normal cases was always less than one centimetre of water per litre per second at this distanding pressure and the peripheral resistance accounted for 25 to 41% of this total. Conversely, the total resistance of the lungs with obstructive airway disease varied from 2.16 to 8.55 cm. H_2O per litre per second and 65-97% of this total was found to be peripheral to the catheter site.

VI. DISCUSSION OF RESULTS

1. Pressure-Volume Studies

The data presented in Table I and the lobar comparisons illustrated graphically in Fig. 5 make several points. No significant differences in pressure-volume characteristics were observed between upper and lower lobes by this method. However, several factors must be taken into consideration in interpreting these data. First, the lobes were expanded from their excised residual volume which is a variable factor and may have influenced the results. Secondly, cases 23302 and 23337 had evidence of traces of emphysema in their upper lobes which may have accounted for the observed differences in lobes from these cases. It is apparent therefore that these data must be considered to be of a preliminary nature. Further investigations are planned in this laboratory to compare the static pressure-volume curves of lobes expanded from the gas-free states with both air and saline. Any observed differences will then be interpreted in the light of tissue and surface forces and careful morphologic investigations will aid in observing the effect of disease.

In Chapter III, 1, A, the work indicating the importance of the static pressure-volume relationship to the distribution of ventilation has been outlined[43,45]. The presented data indicates that there may be regional differences in this relationship and that these differences may be accentuated by minimal amounts of emphysema. The planned investigation outlined in the previous paragraph should help in the understanding of the lobar pressure pressure-volume relationship in both health and disease.

2. Air Transfer Studies

Van Allen and Lindskog[59] were among the first to study collateral air drift across confluent lobar fissures reporting that it occurred only when the cannulated lobe was distended "beyond the normal". Tracings of the pressure-volume and flow-volume relationship from a representative normal case are shown in Fig. 6. These data were recorded simultaneously on a storage oscilloscope so that the pressure producing the flow observed at a particular volume on the right hand figure can be found by observing the pressure at the same volume on the left hand figure. The fact that similar flows are observed at the same volume during inflation and deflation in spite of markedly different pressures at these two positions indicate that the channels must be larger during deflation than inflation. This volume hysteresis of the collateral channels was observed in all three normal cases where attempts to observe it were made.

The data presented in Table II show that collateral air drift was present in five of eight non-emphysematous cases and in seven of eight emphysematous cases. It also illustrates that collateral air drift was present to a larger degree in cases of emphysema. In all cases without emphysema no volume change occurred in the lobe receiving air via collateral channels unless its lobar bronchus was occluded. This observation was similar to those of Van Allen and many others who have studied air drift. However, in our cases of emphysema and bronchitis a marked volume change occurred in the receiving lobe reflecting the bronchial obstruction in this condition. The fact that a large volume change occurred indicates that the obstruction was

between the air spaces which contain the largest proportion of volume and the trachea. An example of this phenomenon is shown in Fig. 7. In this case the distending pressure of the lower lobe is plotted on the horizontal axis while air flow across the fissure is plotted on the vertical axis. A volume change occurred in the upper lobe almost simultaneously with the change in the lower lobe at a pressure of 8 cm. of H_2O but no flow appeared from the upper lobe until a pressure of 15 cm. of H_2O was reached and the lung was nearly fully inflated. This larger pressure represents the force required to overcome the resistance of the upper lobe airways. A comparison of opening pressures of three emphysematous lobes filled both by collateral channels and via the lobar bronchus are shown in Table III. The fact that severely obstructed lobes seemed to fill more easily via collateral channels in incomplete lobar fissures than by their own bronchus raised the possibility that ventilation across incomplete lobar fissures might be important in emphysema. This is best illustrated by case number 23419. In this case the upper lobe was filled from the lower lobe at an opening pressure of 6 cm. H_2O but it was impossible to collect air from the upper lobe bronchus. The same lobe could be filled through its own bronchus but it required a distending pressure of 22 cm. H_2O. Due to the advanced stage of emphysema in the case Fig. 8, it is unlikely that this person could have developed the transpulmonary pressure required to fill the upper lobe via its own bronchus. However, the upper lobe was inflated at necropsy and must have been filled via collateral ventilation from the lower lobe.

The fact that some emphysematous lobes appeared to fill more easily via collateral channels in incomplete lobar fissure than by the lobar bronchus led us to compare the resistance offered by these pathways.

A comparison of this nature is difficult in that there are two variables, the size of the fissure and the size of the channels in the incomplete fissures. The relative completeness or incompleteness of the lobar fissures is a random factor in any series of cases and, since our cases were selected at random from the Autopsy Service of the Department of Pathology, McGill University, fissure incompleteness was thought to be randomly distributed in both the normal and the emphysematous cases. For this reason the marked drop in the resistance offered by the lobar fissure in emphysema was thought to be due to an enlargement of the collateral channels in these fissures. However, it is hoped to get around the difficulty of the size of the uncomplete fissure by studying collateral air transfer from the basal to the apical segment of the lower lobe. Unfortunately, the data that has been collected in these experiments is too incomplete to be presented.

The calculation of resistance to be compared rests on the ability to measure the pressure drop across the incomplete fissure and from the alveolus to the trachea of the lobe receiving the transferred air. This was done in states of steady flow by inserting subpleural catheters and it is believed that these catheters measured pressure in the alveolar spaces for the following reasons. The centre of the secondary lobule is easily defined on the pleural surface as it is outlined by fibrous septa. When the lobule is punctured and the

lung is held at a constant inflating pressure only that lobule collapses. When the catheter tip is then inserted into the puncture hole and fixed so that no leak occurs, the lobule inflates normally. The relationship of the catheter tip to the terminal airways is shown in the bronchogram in Fig. 9 and the fact that it is surrounded by alveoli is shown in Fig. 10. This last demonstration was obtained by removing the catheter in a block of lung tissue and cutting the block directly in front of the catheter tip. Both cut surfaces were then examined under water with a dissecting microscope and photographed. Since there is ample evidence that alveolar walls are incomplete (Chapter III, 2, B), the pressure measured in the false space created by the catheter tip must be the pressure in the alveoli surrounding it during the period of steady flow.

Measurements of resistance across the lobar fissure and out of the lobe receiving transferred air are shown in Table V. This illustrates that the resistance across the fissure is high in normal lungs but drops sharply with emphysema. Cases 23419 and 23456 are included although actual measurements of resistance were not made. However, in these cases there was rapid transfer of air across the fissure which produced a large volume change in the lobe receiving air but no flow at the trachea until very high pressures were reached. The fact that the resistance across the lobar fissure drops in emphysema and the resistance of the lobar airways rise indicate that an incomplete lobar fissure may be an important ventilatory pathway in this condition.

3. Flow Resistance Study

The theoretical aspects of the method have been discussed in Chapters II and III B. This study shows that in normal lungs only a small proportion of the pulmonary resistance is in the small airways. However, the peripheral resistance measured in these human lungs was greater than that reported by Macklem and Mead[28] in dogs. These investigators were able to systematically place the catheter in more peripheral airways. In addition, their investigations were done on living dogs while this data was collected from lungs excised at post mortem where some artifact can be expected. The present results do not necessarily indicate, therefore, that the resistance of the small airways is greater in humans than in dogs.

The fact that the resistance peripheral to the wedged catheter is small is not surprising when considered in the light of the remarkable increase in cross sectional area along the peripheral airways that Weibel[61] has described. Histological sections at the wedged catheter site indicated that the catheters were always wedged in cartilagenous airways. It is thus apparent that the bulk of the lower airway resistance is associated with the cartilagenous airways (i.e. bronchi). Furthermore, from examination of Fig. 12 it is apparent that the peripheral resistance could be doubled in this case without producing a large effect on the total resistance. This means that severe peripheral airway disease could be present without a measurable increase in total pulmonary resistance.

By contrast, the major source of resistance in chronic obstructive airway disease was found in the airways peripheral to the

wedged catheter. This is illustrated by the case of emphysema in Fig. 13 and the case of bronchiectasis in Fig. 14 where the increases in total resistance were mainly due to a large increase in peripheral resistance. Table V demonstrates that the increase in total resistance in all the diseased cases was brought about by a very large increase in the peripheral resistance. In fact the peripheral resistance in the diseased cases varied from five to twenty-four times the largest peripheral resistance observed in the normal cases. The precise reason for this is unclear at this stage but some idea of the severity of small airway disease can be appreciated from Fig. 15. The normal bronchogram, Fig. 15-a, shows extensive filling of small airways near the pleural surface while the abnormal bronchograms (b & c) show a great deal less filling in this area. It is convenient to think of airway disease as fixed or reversible. Reversible small airway disease - plugging with mucopurulent secretions or acute bronchiolitis - was observed in all diseased lungs and undoubtedly contributed to the rise in peripheral resistance. Of the causes of fixed airway disease - bronchiolar narrowing and obliteration, diminished elastic recoil and loss of peribronchiolar alveolar tissue - this study suggests that only bronchiolar narrowing and obliteration are important. Since the measurements reported in normal and abnormal lungs were made at similar distending pressure loss of elastic recoil cannot explain the results. If loss of alveolar support was a major cause of airway obstruction so that the outer walls of the bronchioles were exposed to alveolar pressure rather than pleural pressure[22] one could expect peripheral resistance to be greater on inspiration than on expiration. No systematic difference of this sort was observed during lung oscillation. Fixed bronchiolar

narrowing and obliteration were striking histologic features of both the cases of bronchitis and emphysema and the case of severe bronchiectasis. The fixed component of the increase in peripheral resistance is thus attributed to bronchiolar narrowing and obliteration.

VII. SUMMARY

The general literature on lung mechanics and collateral air transfer has been reviewed and the morphologic literature on emphysema and bronchitis highlighted. The literature pertaining to morphologic and mechanical measurements made in emphysema was then considered in detail.

An investigation into the following mechanical properties of excised human lungs has been reported: The pressure-volume characteristics of upper and lower lobes from seven lungs, air transfer across lobar fissures in eight non-emphysematous and eight emphysematous lungs, and the partitioning of pulmonary resistance in four normal cases, four cases with bronchitis and emphysema and one case with severe varicose bronchiectasis.

VIII. CONCLUSIONS

1. No absolute conclusion could be drawn concerning the difference in pressure-volume characteristics between upper and lower lobes. Preliminary data reported here indicate that this area of investigation will be fruitful.

2. Collateral air transfer across incomplete lobar fissure occurs in normal excised lungs. Contrary to previous reports[59], air transfer can occur out of a lobe in its normal volume range. However, the resistance to air transfer by this method is high.

3. In emphysema, collateral air transfer across lobar fissures is greatly increased. The resistance across the fissure is very much lower than in normal lungs and was found to be less than the resistance of the lobar airways in four cases of emphysema.

4. Air transfer into an emphysematous lobe produces a volume change in that lobe. This was not the case in the normal lungs reported here nor in those reported by others[59]. This fact is a reflection of the airway obstruction present in this disease and the fact that this volume change was large indicates that the obstruction was likely proximal to the alveolated structures proceeding from trachea to alveolus.

5. In normal lungs, the bulk of the pulmonary resistance was attributed to the bronchi.

6. In the four cases of bronchitis and emphysema and the case of severe bronchiectasis studied with retrograde catheters, the main source of resistance was in the airways smaller than 3 mm. internal diameter. This was attributed to mucopurulent plugging and acute bronchiolitis along with narrowing and obliteration of many small airways by chronic inflammation.

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Table I

Pressure-Volume Data From 7 Lungs

A. Upper Lobe - Pressure (cm. H_2O)

Case No.	2	5	10	15	20	30
23302	17	40	67	81	92	100
23337	28	56	80	90	96	100
23350 R	37	57	78	88	96	100
L	15	46	73	88	96	100
23438 R	37	64	79	95	97	100
L	32	60	84	92	96	100
23490	38	55	77	91	97	100
Mean	29	54	77	89	96	100

Volume % lobar vital capacity

B. Lower Lobe - Pressure (cm. H_2O)

Case No.	2	5	10	15	20	30
23302	7	23	63	87	96	100
23337	14	45	74	87	96	100
23350 R	23	47	74	88	95	100
L	26	50	76	88	96	100
23438 R	21	57	82	93	97	100
L	17	52	79	88	96	100
23490	33	50	72	89	95	100
Mean	20	46	74	89	96	100

Volume % lobar vital capacity

C. Emphysema Scores

Case No.	302	337	(R) 350	(L) 350	(R) 348	(L) 348	490
Subjective[1] Index 0-30	2 UL	2 UL	0	0	0	0	0
Point Count[2] %	5.8	5.9	1.0	1.0	1.0	1.0	1.0

(1) & (2) - see Legend Table II.

Table II

Case No.	Age	Sex	Point Count % Involvement (1)	Subjective Index (0-30) (2)	Air Transfer L-U Lobe (Litre/sec.) (3)
23316 R	52	M	< 1.0	0	0.025
23325 L	33	M	< 1.0	0	- (4)
23350 L	19	M	< 1.0	0	0.076
23430 L	45	M	< 1.0	0	0.025
23438 R	31	F	< 1.0	0	-
23490 L	63	F	< 1.0	0	-
23609 L	67	F	< 1.0	0	0.005
23630 L	72	F	< 1.0	0	0.020
23302 R	52	M	5.8	2	0.260
23337 R	73	F	5.9	2	0.150
23419 L	73	M	87.3	17	Large (5)
23456 R	59	M	95.3	18	0.400
23506 L	70	M	60.9	14	Large (5)
23518 R	53	F	51.4	14	-
23620 L	58	M	41.0	16	0.100
23633 R	80	M	47.2	10	0.500

(1) Point Count. Thurlbeck's modification of Dunnill's method (13) (Counts done by the author).
(2) Subjective Index. Thurlbeck's subjective index (57) (Grade assigned by Dr. W.M.Thurlbeck)
(3) Air Transfer measured at a distending pressure of 20 cm. H_2O in litres/sec. from the lower to the upper lobe.
(4) Indicates no air transfer at any distending pressure.
(5) Air Transfer was large but not accurately measured at the trachea due to trapping of air in the upper lobe.

Table III

Opening Pressures of Emphysematous Lobes Via the Lobar Bronchus and the Lobar Fissure

Case No.	Emphysema Score		Upper Lobe Opening Pressure (cm/H_2O)	
	Point Count %[1]	Subjective Index (0-30)[2]	Via Upper Lobe Bronchus	From the Lower Lobe via Channels in the Lobar Fissure
23419	87.3	17	26	6
23456	95.3	18	15	8
23518	51.4	14	12.5	7.5

(1) & (2) - see Legend Table II.

Table IV

Resistance to Air Transfer Into a Lobe Across the Lobar Fissure Compared to the Resistance of Flow Out of That Lobe

Case No.	Resistance to Air Transfer cm H_2O/LP.S.		Emphysema Grade	
	Lower Lobe to Upper Lobe	Upper Lobe to Trachea	Point Count (1)	Subjective Index (2)
33316	3000	0_+^*	1%	0
23306	2000	0_+	1%	0
23630	925	0_+	1%	0
23302	108	0_+	5.8%	2
23620	10	80	41.0%	16
23633	20	10	47.2%	10
23419	?**	∞***	87.3%	17
23506	?	∞	60.9%	14

*0_+ Greater than 0 but too small to measure.

**? Resistance not measured but thought to be small as rapid transfer of air was observed from lower to upper lobe.

***∞ Large resistance as air was trapped in upper lobe where it produced a rapid volume change.

(1) & (2) - see Legend Table II.

Table V

Resistance at Transpulmonary Pressure of 5 cm. H_2O

(cm. H_2O/LPS)

	Case No.	Generation*	R_L	R_P	$\frac{R_P}{R_L}$ %
Normal	23316	11	0.75	0.31	41
	23350	7	0.76	0.29	38
	23430	9	0.44	0.11	25
	23438	7	0.57	0.19	33
Emphysema	23419	7	8.55	7.5	88
	23456	5	2.22	1.67	75
	23506	8	2.16	2.10	97
	23518	7	3.71	2.42	65
Bronchiectasis	23239	9	3.80	2.90	76

*Lobar = 1.

Comparison of peripheral to total resistance in normal and diseased cases.

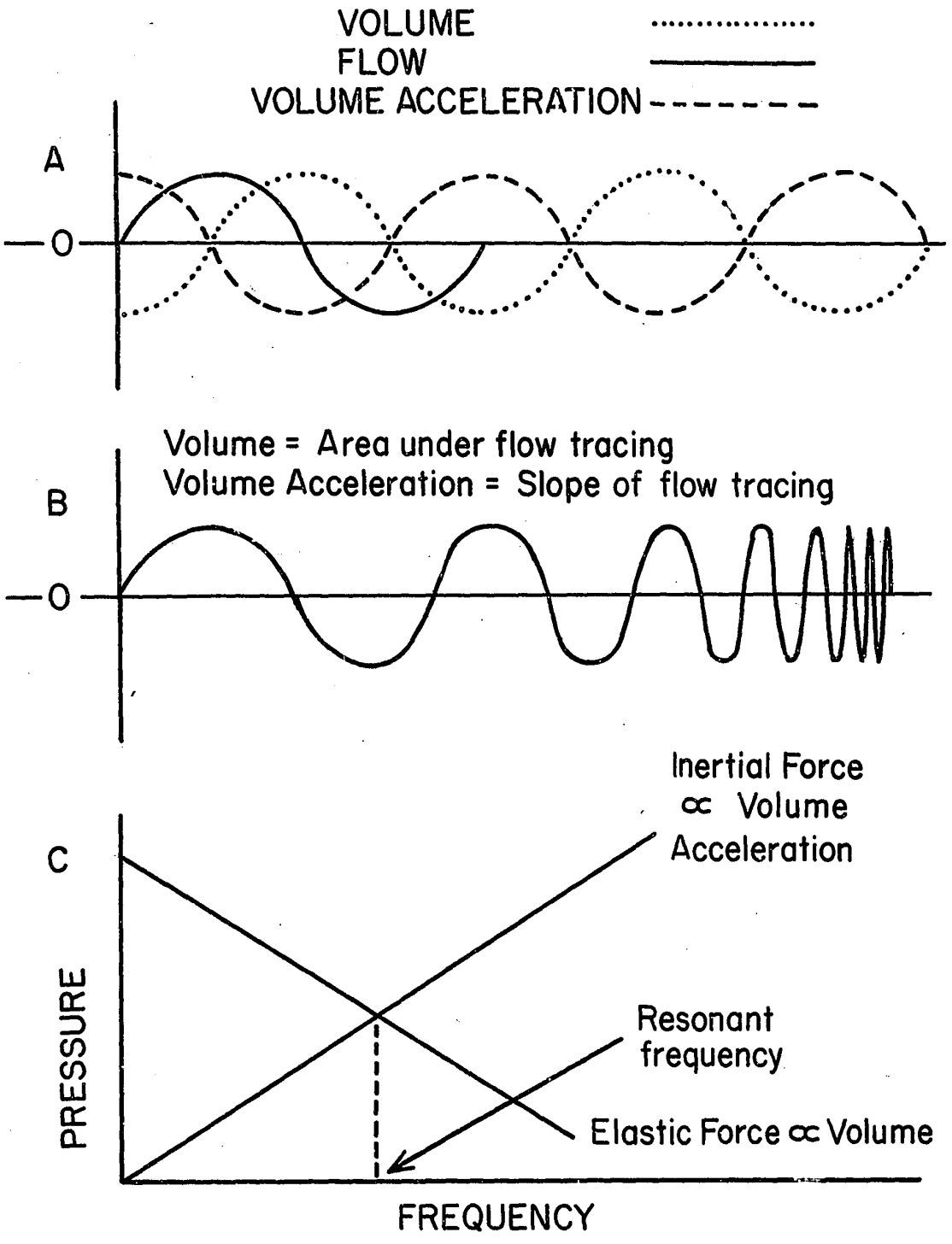


Fig. 1. (a) Illustrates that volume and volume acceleration are 180° out of phase with each other.
(b) Illustrates that volume decreases and volume acceleration increases with increased frequency.
(c) Illustrates that at a particular frequency inertial and elastic forces are equal.

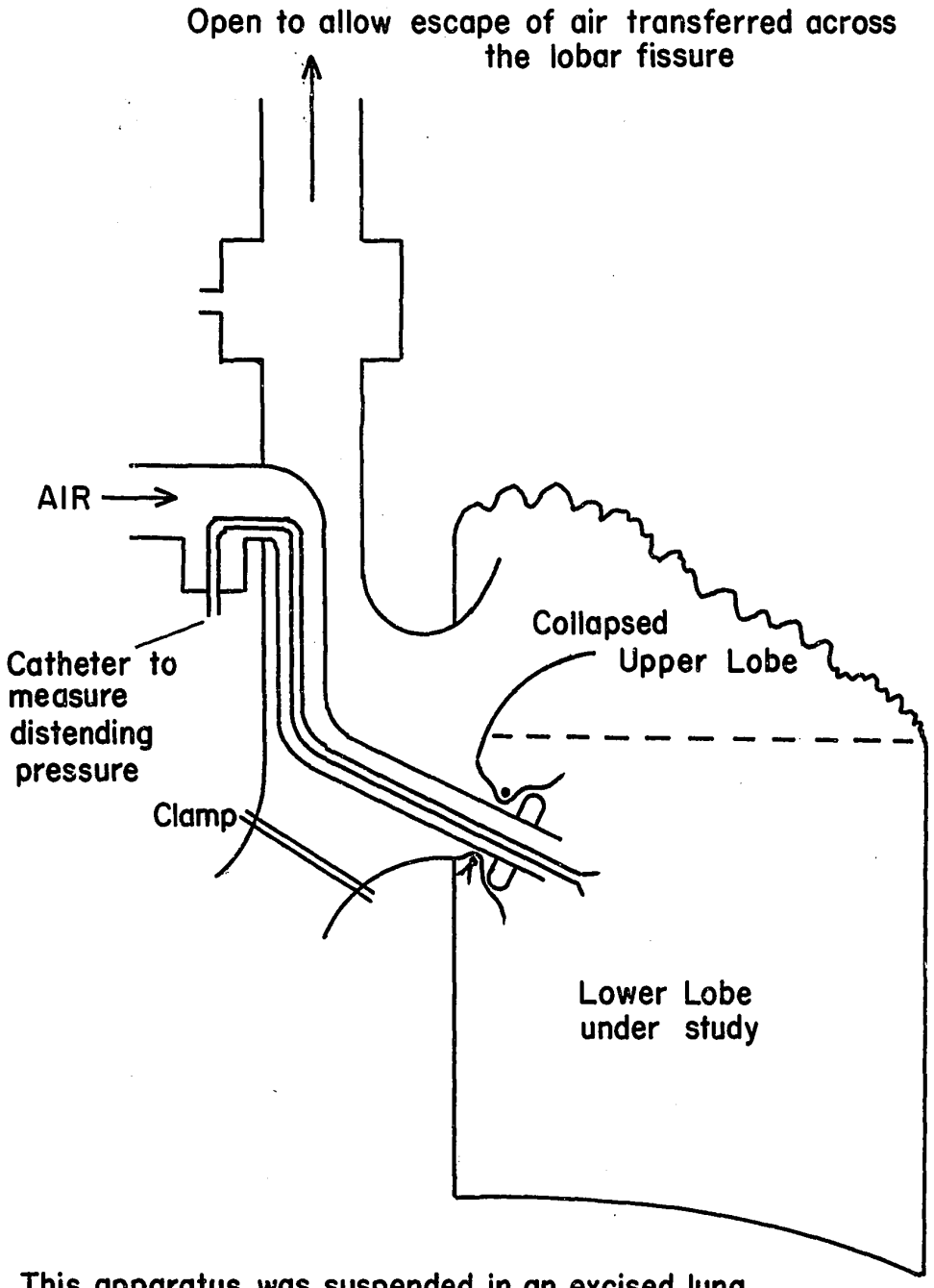


Fig. 2. Apparatus for measuring lobar pressure volume curves.

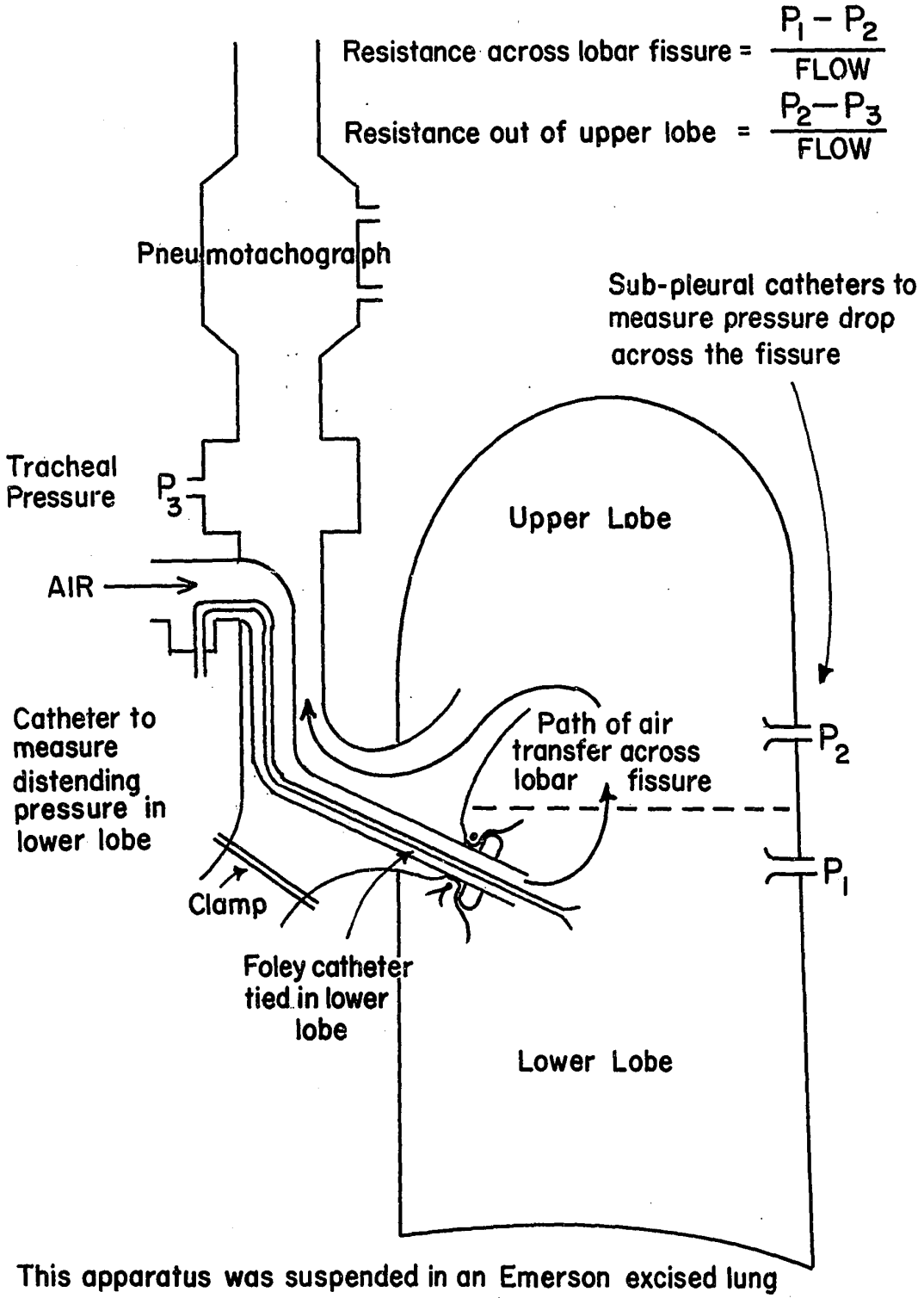
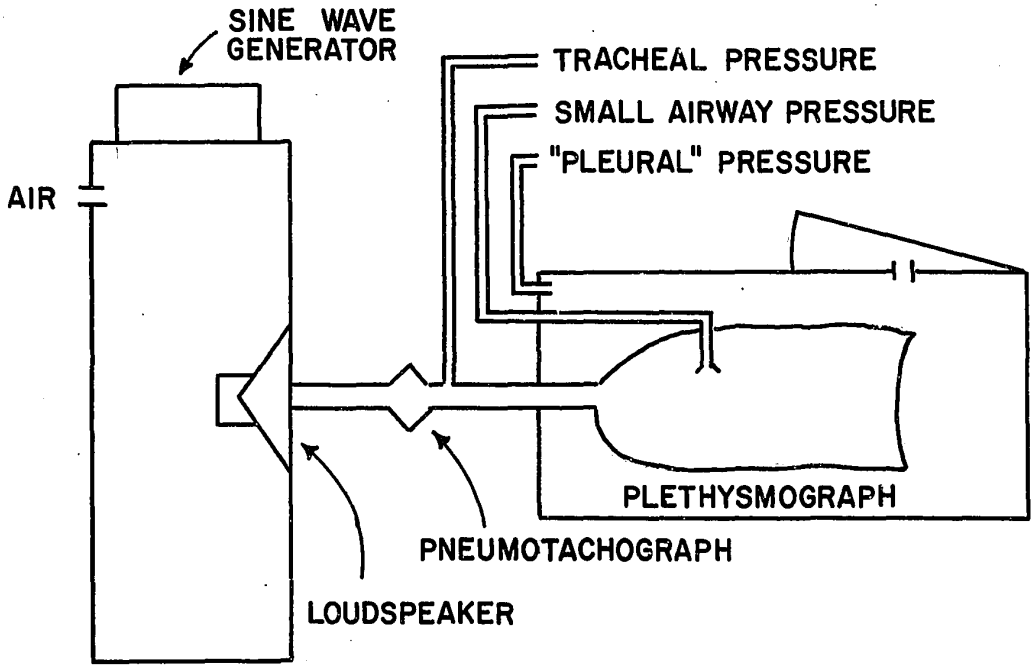


Fig. 3. Apparatus for measuring air transfer across the lobar fissure.



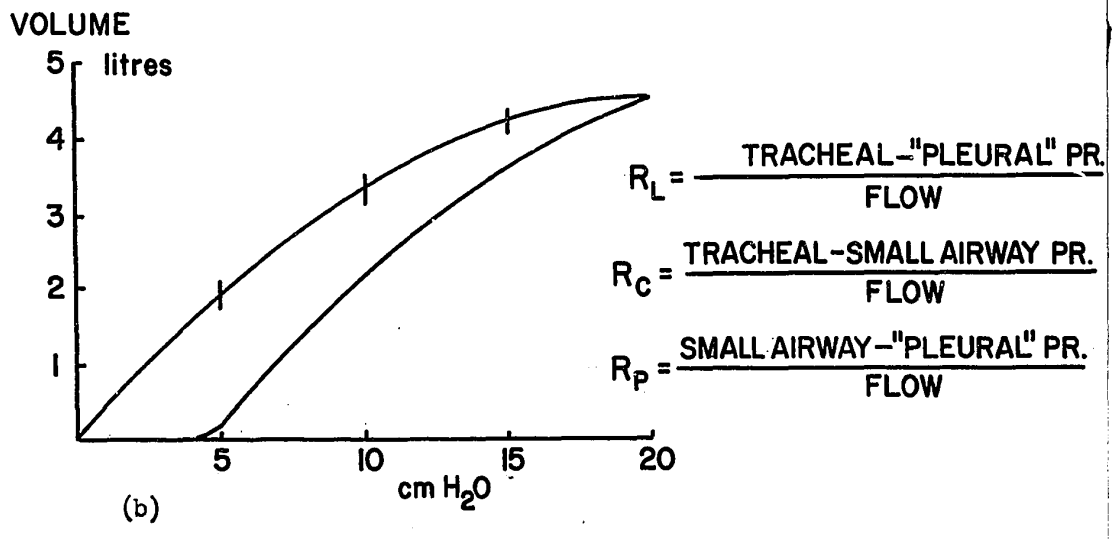


Fig. 4. (a) Apparatus for partitioning of airway resistance.

(b) Resistances were measured in the deflation limb of the pressure volume curve. R_L refers to total resistance, R_C and R_P to the resistance central and peripheral to the catheter tip.

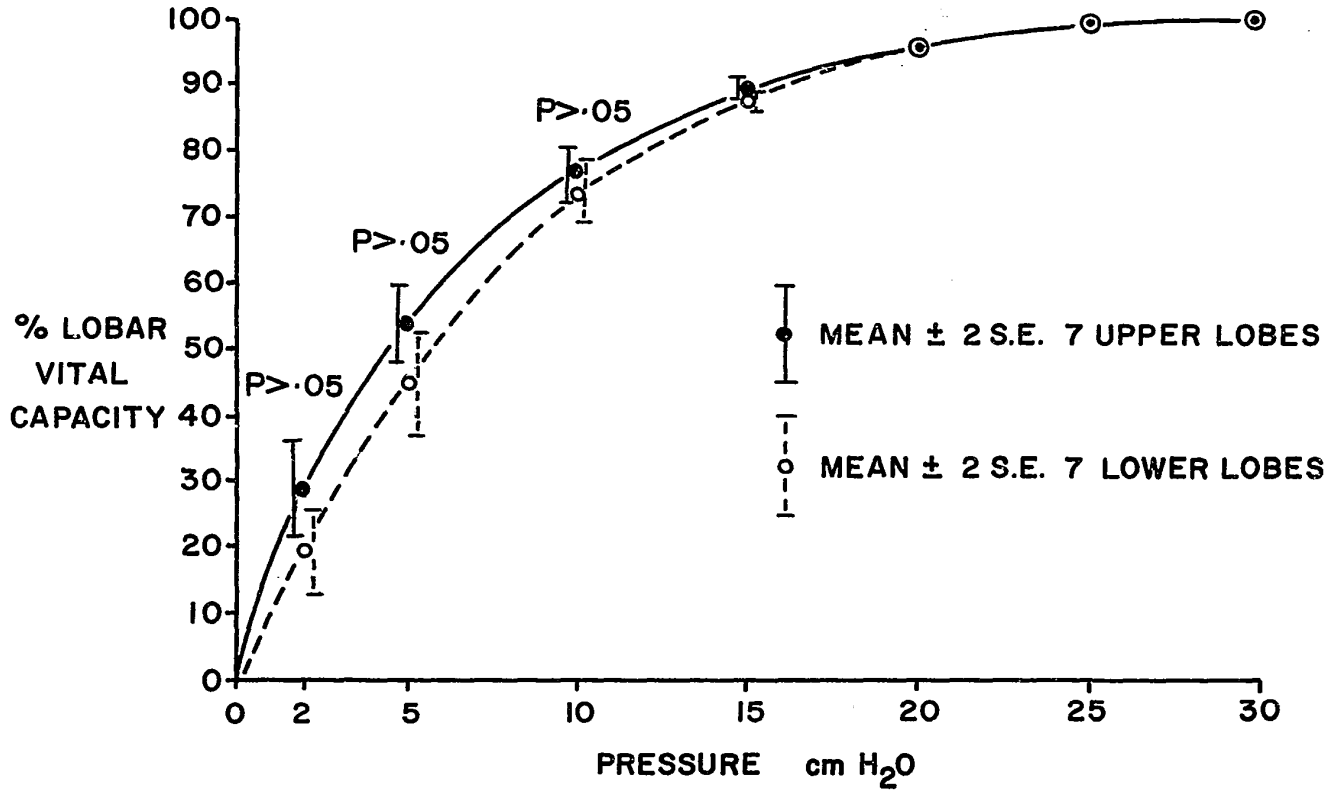


Fig. 5. Comparison of upper and lower lobe pressure volume curves.

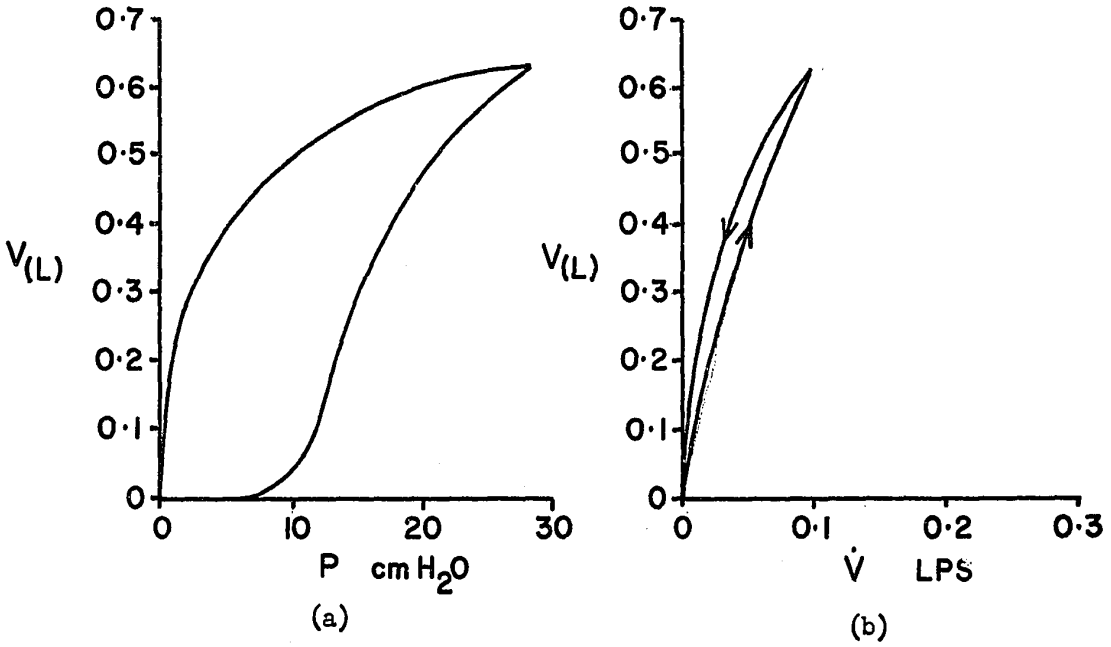


Fig. 6. Lobar volume $V_{(L)}$ plotted simultaneously against: (a) distending pressure and (b) collateral flow leaving the lobe during a single inflation and deflation of a normal lobe.

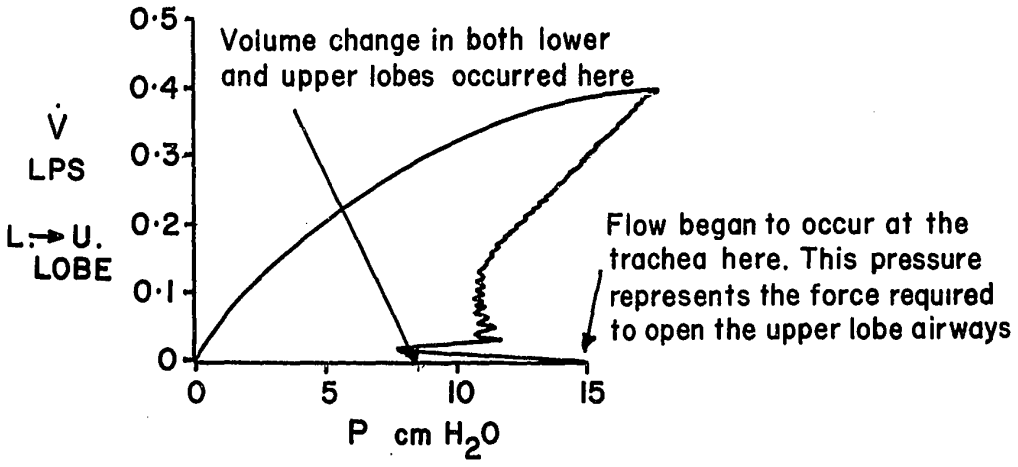


Fig. 7. Illustrates air trapping in an emphysematous lobe receiving air drift. Flow from the lower to the upper lobe produced a volume change in the upper lobe before any flow appeared at the trachea.

FIGURE 8: Whole lung section of case 23419 which demonstrated large translobar air transfer.

FIGURE 8: Whole lung section of case 23419 which demonstrated large translobar air transfer.

FIGURE 9: Demonstrates the relationship of the subpleural catheter to the peripheral airways.

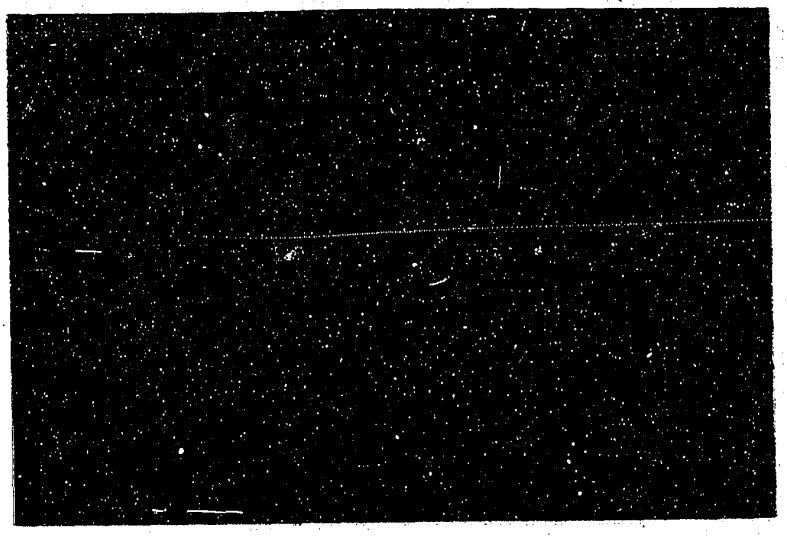
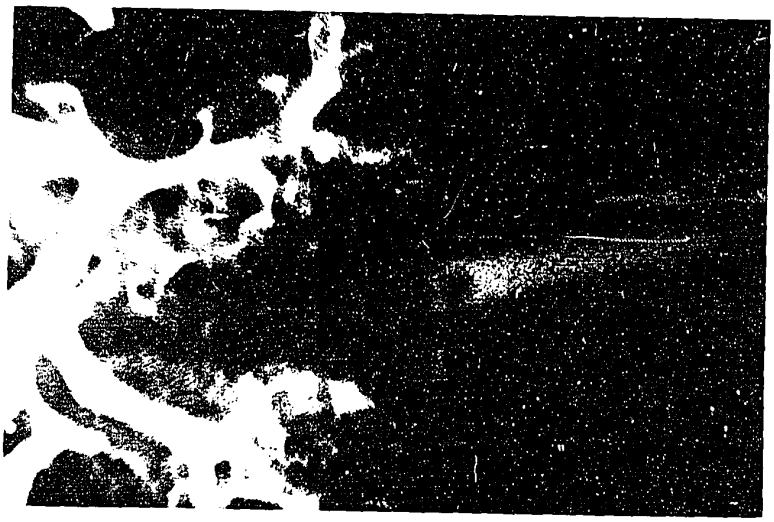


FIGURE 10: Demonstrates the relationship of the subpleural catheter tip to the alveoli (photographed under water with a dissecting microscope).



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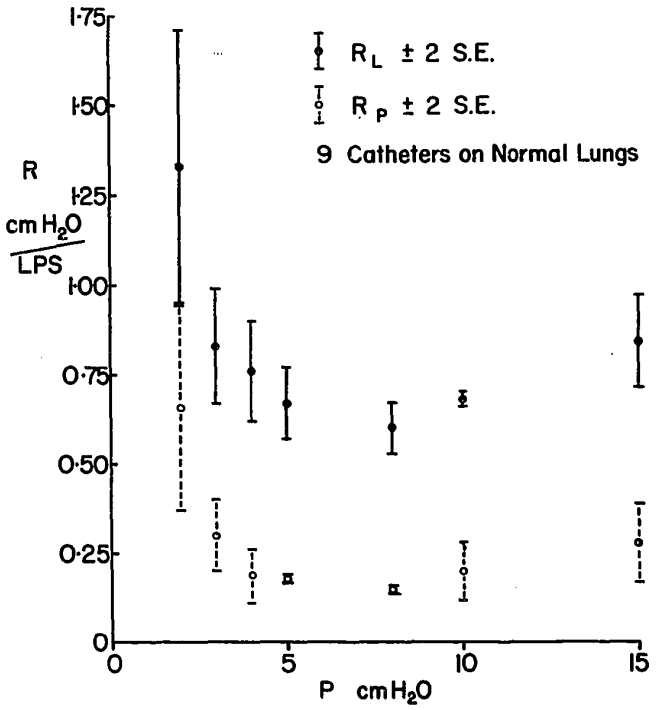


FIGURE 11: Results of 9 retrograde catheters from four normal cases. Closed circles and solid bars represent mean ±2 standard excess of the total resistance. Open circles and hatched bars represent mean ±2 standard errors of the peripheral resistance.

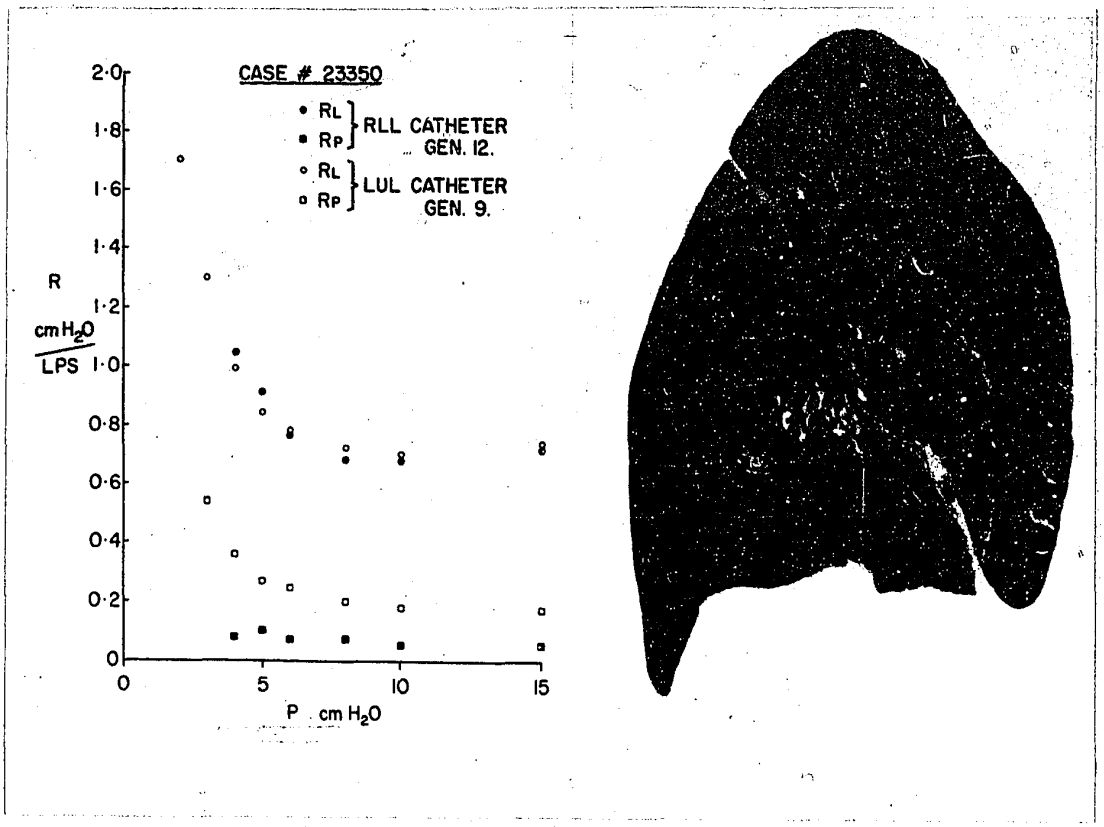
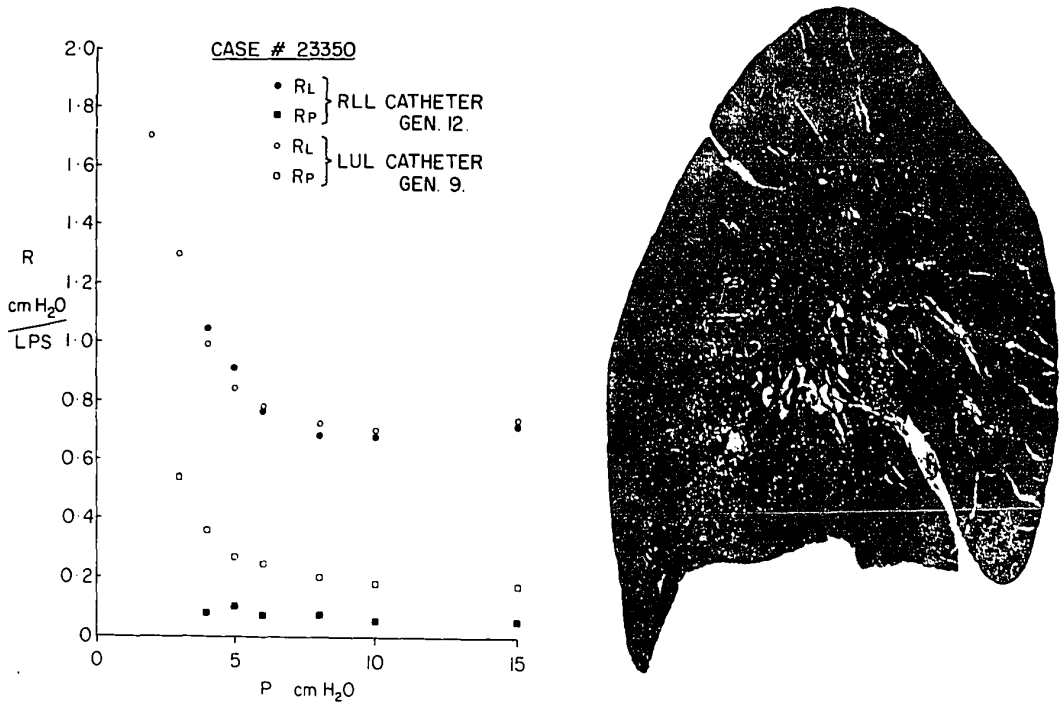


FIGURE 12: Results of 2 retrograde catheters from a normal case. Illustrates that (a) Peripheral resistance becomes smaller as the catheter is placed further out in the bronchial tree (b) that the resistance of the small airways could be doubled without a noticeable change in the total resistance.



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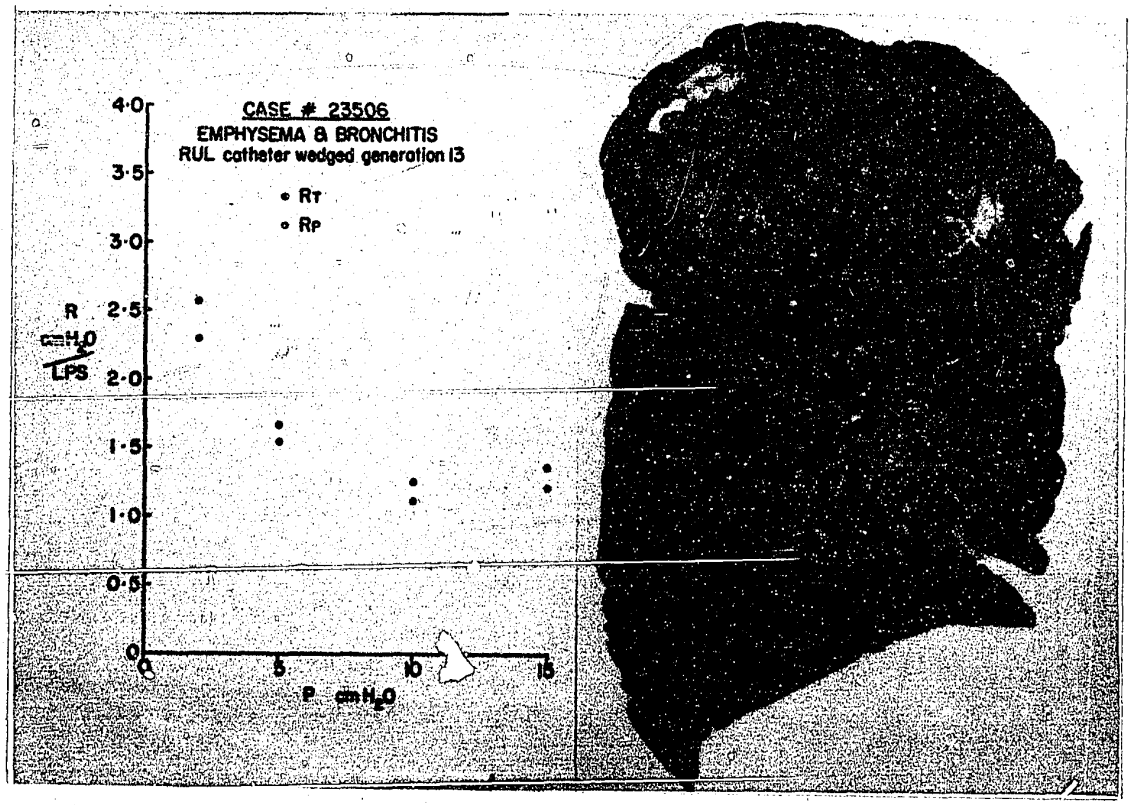
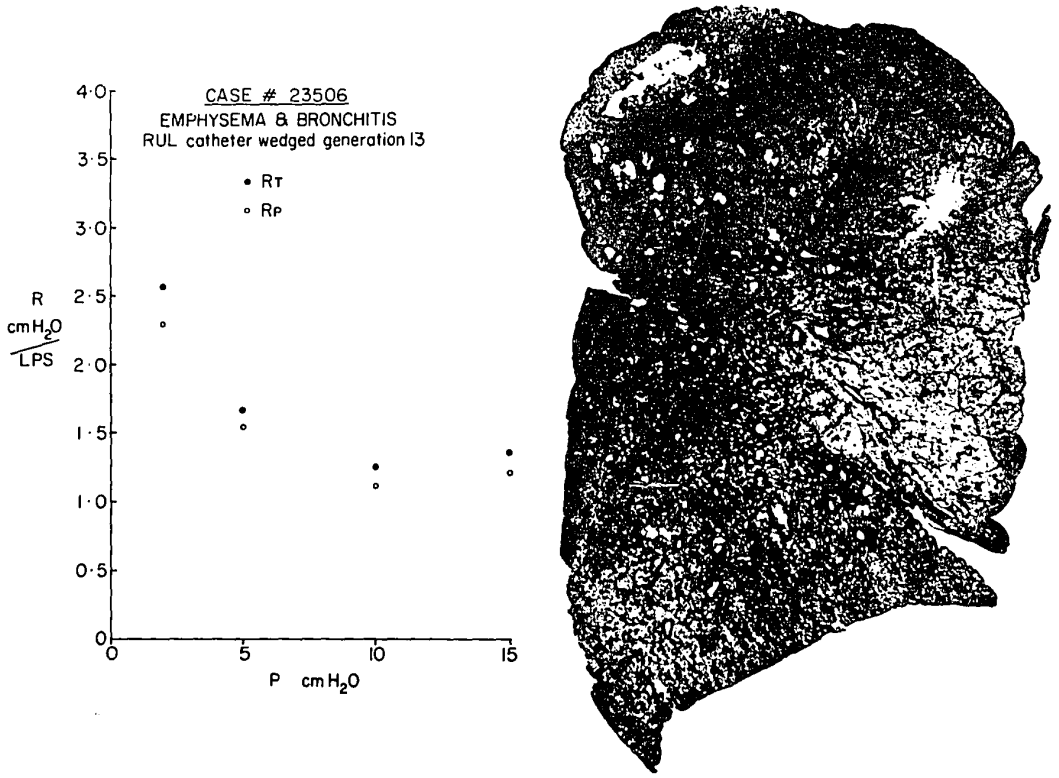


FIGURE 13: Retrograde catheter data and whole lung section from a representative case of emphysema. Note the large increase in peripheral resistance.



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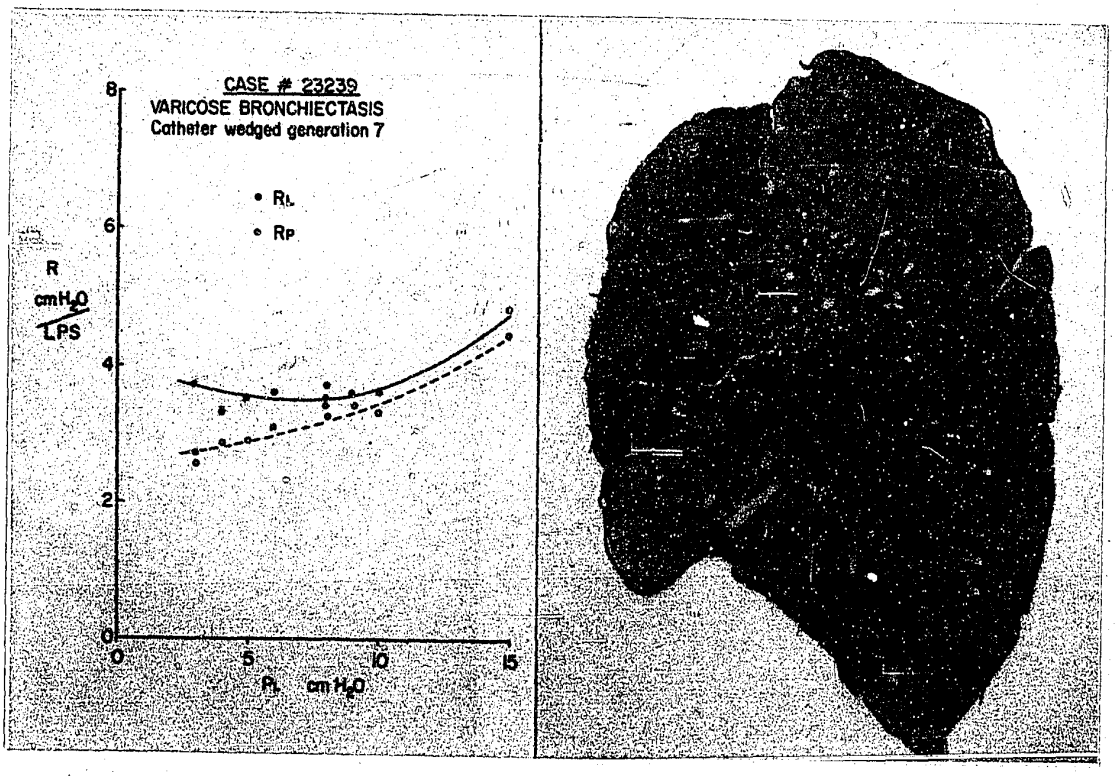
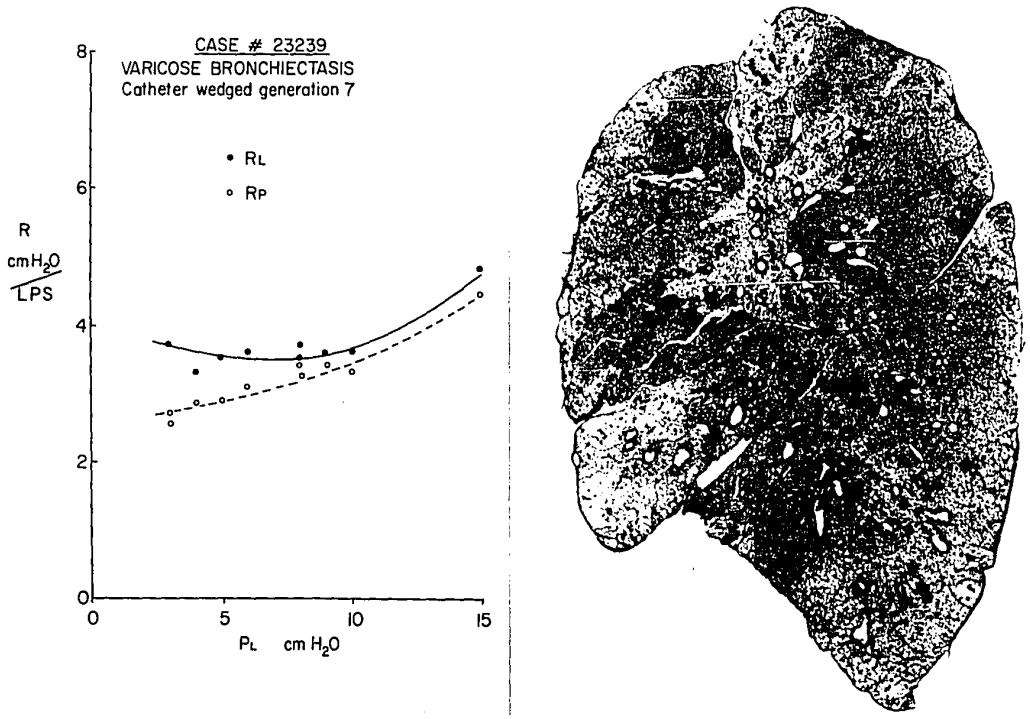


FIGURE 14: Retograde catheter data from a case of severe varicose bronchiectasis. The increase in total resistance is due to a large increase in peripheral resistance.



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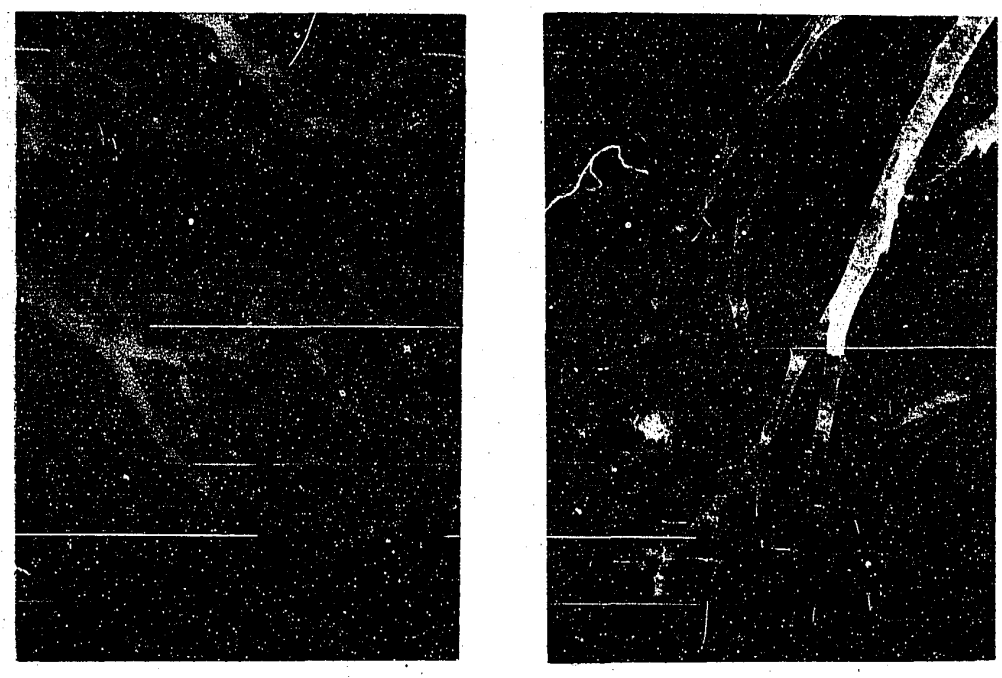
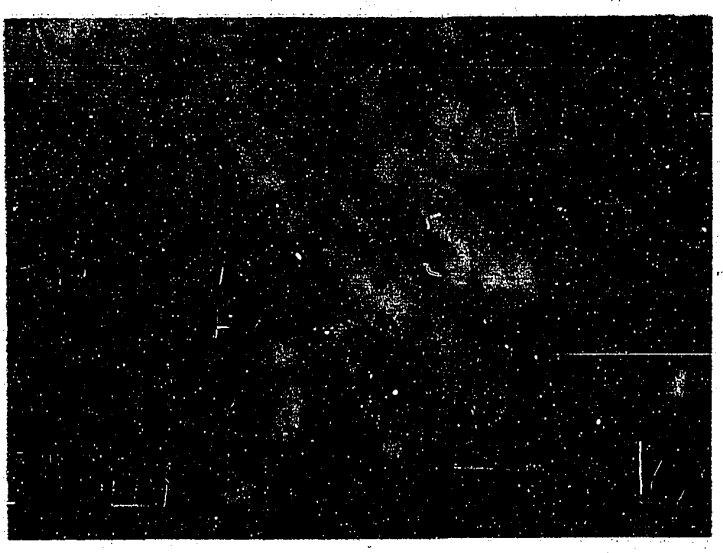
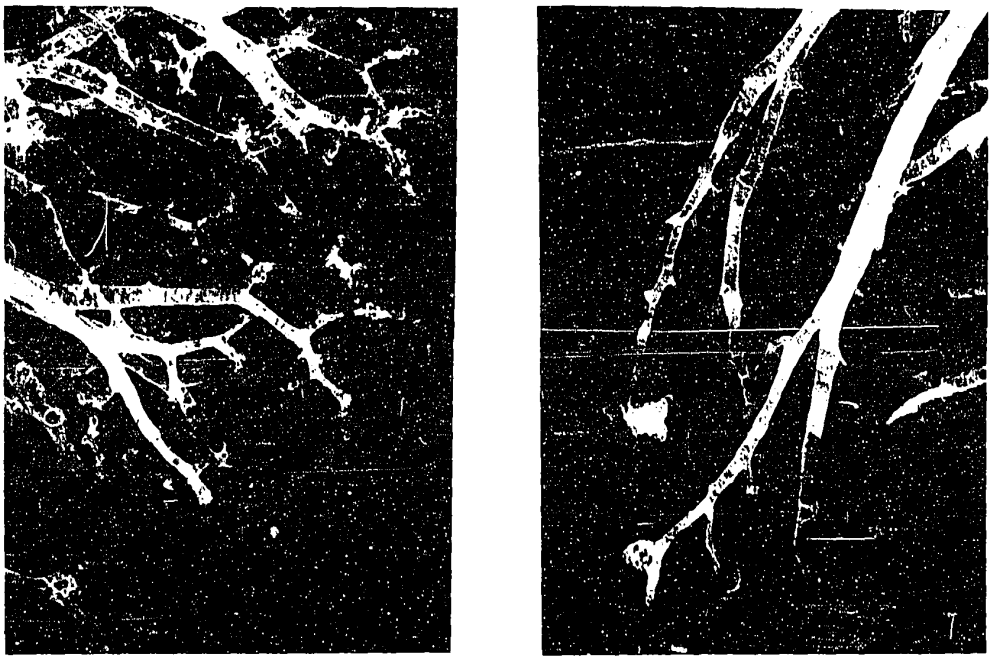


A B

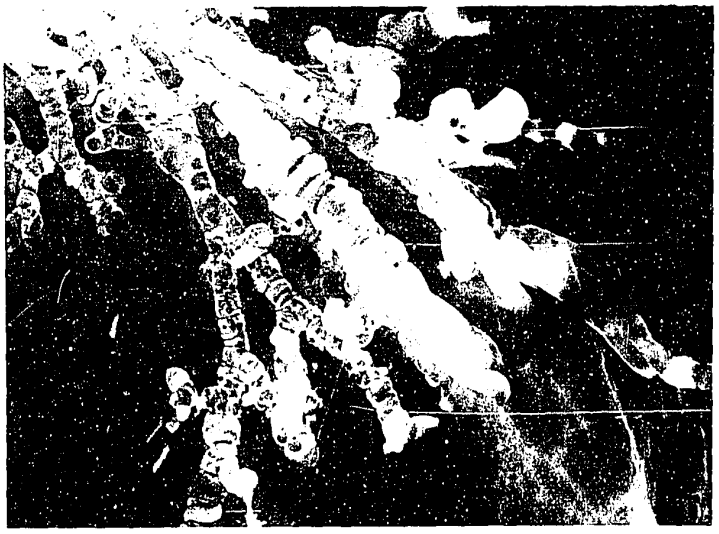


C

FIGURE 15: Bronchograms A) Normal B) Emphysema C) Bronchiectasis. Note decreased filling of small airways in (B) and (C).



A B



C

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