M.Sc. Department of Experimental Medicine

ABSTRACT

EXPERIMENTAL PULMONARY EMPHYSEMA IN DOGS

by

RUNGSUN PUSHPAKOM, M.D.

Varying degrees of panlobular emphysema were produced in 10 dogs by intratracheal injection of papain. Pulmonary function was studied before and after the development of emphysema. The production of emphysema led to an increase in FRC, RV and TLC of 23%, 24%, and 16% respectively. The arterial oxygen saturation decreased by 8% and the Pao_2 by 19 mmHg. There was no significant effect on the $Paco_2$, pH and bicarbonate. Steady state diffusing capacity was reduced by 55%, compliance increased by 63% and there was a shift in the static pressure volume curve of the lung upward and to the left. The relationship between pulmonary resistance, R_L, and lung volume was not significantly changed. However, following excision of the lungs, R_L was partitioned by the retrograde catheter technique and the peripheral resistance was abnormally high accounting for 33 to 84% of R_L. There was a decrease in the resistance of the central airways explaining the preservation of a normal R_L. Trivial to moderate panlobular emphysema was found in the animals and was usually fairly localized in extent. Mean linear intercept ranged from 0.124 to 0.258 (normal 0.009 - 0.149). The alveolar surface area at a standard lung volume was reduced to 33.0 - 57.0 m^2 (normal 59 - 71 m^2). With the exception of FRC there was no significant correlation between any of the function tests and the degree of emphysema.

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ABSTRACT

Varying degrees of panlobular emphysema was produced in 10 dogs by intratracheal injection of papain. Pulmonary function was studied before and after the development of emphysema. The production of emphysema led to an increase FRC, RV and TLC of 23%, 24%, 16% respectively. The arterial oxygen saturation decreased by 8% and the Pao_2 by 19 mmHg. There was no significant effect on the $Paco_2$, pH and bicarbonate. Steady state diffusing capacity was reduced by 55, compliance increased by 63% and there was a shift in the static pressure volume curve of the lung upward and to the left. The relationship between pulmonary resistance, R_L, and lung volume was not significantly changed. However, following excision of the lungs, R_L was partitioned by the retrograde catheter technique and the peripheral resistance was abnormally high accounting from 33 to 84 of R_L. There was a decrease in the resistance of the central airways explaining the preservation of a normal R_L. Trivial to moderate panlobular emphysema was found in the animals and was usually fairly localized in extent. Mean linear intercept ranged from 0.124 to 0.258 (normal 0.009 - 0.149). The alveolar surface area at a standard lung volume was reduced to 33.0 - 57.0 (normal 59 - 71). With exception of the FRC there was no significant correlation between any of the function tests and the degree of emphysema.

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INTRODUCTION

Although pulmonary emphysema has been extensively studied in recent years, close correlations between lung structure and function are impossible in patients with this disease. Although attempts at correlating anti mortem function with morphology obtained at post mortem examination have been helpful, they are often difficult to interpret at the conditions at the time of study and are usually quite different from those at the time of death. It is therefore obvious that an experimental model of emphysema in an animal large enough for adequate physiological studies would be of great value. The data presented in this thesis represents an attempt to create such a model in the dog.

Histological Review

Since vesicular and interstitial emphysema was first recognized and described by Laennec (66), in 1819, a number of studies on the disease have been reported. Many attempts to produce emphysema experimentally have been carried out on animals.

The pioneer investigator who claimed to produce emphysema in dogs and rabbits was Brown-Sequard (16). Stimulation of the vagus nerve or its central nuclei resulted in pulmonary distention and he concluded that the disease had been produced by a bronchial spasm, which forced air through the lumen into the terminal alveoli. These experiments lasted only a few days, and no objective evidence of his results was presented. Current opinion does not accept that the alveoli in these lungs are emphysematous.

Köhler (60, in 1877, narrowed the trachea of twenty rabbits with a ligature. He found that pulmonary alveoli were dilated histologically 3 to 4 weeks after ligation. The method of partial ligation of the trachea was also used by Sudsuki (112), in 1899. Only three out of nine rabbits survived between 46 and 84 days and tracheal stenosis was found at necropsy. Pulmonary emphysema was diagnosed from the gross and microscopic examination of the lungs.

In 1900, Bullara (17) by obstructing the nares of three dogs, claimed to have produced emphysema. But the diagnostic criteria wwere not well defined. In 1909, Schall (106) used a special mask with an adjustable valve, that could be regulated to obstruct expiration or inspiration in dogs. Obstructive breathing was imposed on two dogs, one during inspiration

and the other during expiration for a period of nine and ten and a half months, respectively. In two other animals, the obstruction was produced in the same way but it was so great that the dogs expired a few hours after the masks were applied. Histologic study of the lungs of all animals showed no pulmonary emphysema. In a series of acute experimental studies of the carbon dioxide content of alveolar air and in the blood during expiratory obstruction with a one-way valve in the trachea, Friedman and Jackson (43) reported the presence of emphysema. The experiments lasted three to eight hours and histologic examination of the lung tissue showed dilated and ruptured alveoli.

In 1919, Kelman (58) inflated the lungs of 7 rabbits with intermittent positive pressure of varying duration. He also produced respiratory distress, as seen in the disease, by means of anaphylactic shock and by infecting the lung with the broth of influenza virus in another three animals. He claimed that marginal vesicular emphysema was present in the lungs of these animals.

Harris and Chillingworth (50), in the same year, attempted to produce emphysema by placing ball valves in the tracheas of 25 dogs for periods of 24 hours to 3 weeks. A gradual and prominent enlargement of the thoracic cavity was observed. During mild exercise and the presence of an irritant, the dogs became more dyspneic.

At necrospy, the lungs were reported to show typical human pulmonary emphysema. The organs were distended with no tendency to collapse but no mention was made of the removal of the ball valves. The

The alveolar walls were thin and ruptured.

In 1927, Nissen (88) enlarged the thoracic cavity of 12 dogs by placing a metal bar between the cut ends of the ribs and sternum. Six of the dogs died within the first day and the rest were killed within a short time. None of these dogs showed any evidence of emphysema. Further attempts were carried out on three dogs, four rabbits and three cats by means of tracheal stenosis. After three to six months of ligation, emphysema was found to be present in small scattered areas of the lungs of these animals. In another group of animals, ligation of the main bronchus or the right and left pulmonary artery caused atelectasis of the involved portion of the lung. The remaining aerated portion showed chronic compensatory emphysema.

During a study on the effect of oxygen tension on the lungs of cats, monkeys, rabbits, rats and mice, Campbell (18) noted that emphysema followed acclimatization to low oxygen pressure, and he thought that hyperpnea was the cause.

Loeb (70), in 1930, produced partial stenosis of the trachea by placing a plug with a small hole into the trachea of dogs. Eight surviving dogs were sacrificed at two months intervals during a fourteen month period. Gross and microscopic examination of the lungs showed insignificant parenchymal changes.

In 1932, Prodan (97) reported a series study on the toxicity of cadmium. Eleven cats were exposed to cadmium, fumes of cadmium oxide,

dust of cadmium oxide or cadmium sulphate. Emphysema was found in the cat lungs after a twenty-four hour low dose exposure.

Adamsand Livingstone (1), in 1932, performed lobectomy and pneumonectomy on twenty-eight dogs which after producing a complete stenosis of the pulmonary lobe bronchus by the intrabronchial application of the silver nitrate. The animals were sacrificed during a time period from two months to a year following the above procedures. On examination of the lungs, compensatory emphysema was found.

In 1933, Prinzmetal (95), placed a number of rats into a tank in which the pressure was reduced to 350 to 450 mm Hg. which kept them hypoxic. After periods of one to ten weeks, the rats were sacrificed. Microscopic examination showed markedly distended alveoli and broken walls.

Rienhoff, Reichert and Heuer (103), in 1935, studied the detailed effect of pneumonectomy on the remaining lung tissue. They used the technique of injection, corrosion and a wax plate re-construction to observe the changes in the bronchial tree and the terminal respiratory units. The alveolar changes were observed histologically. The study was done six months after pneumonectomy. They concluded that the changes at the residual lungs were due to a simple dilatation of the respiratory lobule.

Kountz, Alexander and Prinzmetal (62), in 1936, used the technique of Adams and Livingstone (1) to produce emphysema in nineteen dogs in their experiments on the effect of the disease on the heart.

About 80% of the lung was removed by pneumonectomy. Compensatory emphysema was also found in the remaining lung portion.

In 1938, Hinshaw (55) introduced a special ball valve into the trachea of dogs to cause more obstruction during expiration than during inspiration. The valves were left in place for some months after which the animals were sacrificed. Emphysema was claimed to have been produced but Hinshaw gave no details on pathological changes.

Paine (90), in 1940, developed an intratracheal hinge valve, placed in the trachea of dogs and which obstructed expiratory or inspiratory breathing. The distensibility coefficient was used as an objective parameter for evaluating the results. He found that distensibility had increased and that the dog lungs definitely had emphysema either during inspiratory or expiratory obstruction.

Paine increased the volume of the thorax in other dogs by plicating the diaphragm. He reported that the coefficient of pulmonary distensibility was consistently elevated. The alveolar walls of the lungs had fragmented and atrophied with the resultant formation of large dilated air spaces.

Rasmussen and Adams (100), in 1942, thought that an elevation of intrabronchial pressure would be a cause of emphysema. They proved it by bi-weekly over inflation of the lungs of seven dogs with an intermittent positive pressure of 30 - 35 mm. Hg. for a period up to eleven months. Vesicular emphysema was observed in only one animal.

Longacre and Johansmann (67), in 1940, reported the effects of pneumonectomy on the residual lung of three young and two adult dogs. After a period of 2 to 4 years they observed a reduction of the elastic recoil, as shown by the less negative intrapulmonary pressure. Histological measurement revealed that the mean diameter of the alveoli was increased and that alveolar walls were broken in animals operated upon as adults. However, the mean diameter of the alveoli in puppy lungs was decreased. Therefore, this indicates hyperplasia of alveoli.

In 1959, Krahl (63) inserted a plastic ball valve in the right lower lobe bronchus of ten adult rats to increase the expiratory resistance of the region. After 18 - 71 days, the lungs were found to contain inflamed airways and dilated alveoli with degeneration of their walls and a decrease in elastic fibers. He concluded that emphysema was caused by both inflamation and air trapping.

Crowle (25), in 1959, produced immunological damage to the lungs of three guinea pigs. He treated the animals with a homologous damaged lung tissue taken from animals killed slowly with nitrogen oxide gas. After five weeks of treatment gross and microscopic examination revealed the lung to be bright red in colour and appear to retain more air. Although the findings were not conclusive, blebs, consisting of stretched and degenerate alveolar septa, were accompanied by a surrounding hyperemic congestion.

By injecting Caledon blue R-C into the ear veins of 25 eight or nine month old rabbits, Strawbridge (111) was able to produce ischemia.

The particles lodged in the precapillaries and capillaries, thereby causing ischemia. The animals survived for between one to twenty-four weeks. The emphysema was assessed by the extent and severity of the destruction of lung tissue by fenestration. The generalized and subpleural emphysema was found to be identical to human chronic emphysema. He concluded that chronic emphysema is an ischemic atrophy of lung tissue.

Frayser (42), in 1963, placed a ball valve in the lobar bronchus of 8 dogs which were partially obstructed during expiration. Pulmonary function measurements as well as pathological evidence was used to evaluate the results. Sixteen to nineteen weeks after placement of the valve, only three of the eight animals which had evidence of infection superimposed on the obstruction, showed an increase in FRC and a small alteration of the blood gases and of pulmonary compliance. The lung tissue of six of the eight animals showed histological changes which resembled those found in human emphysematous lungs.

Kleinerman and Wright (59), in 1962, exposed guinea pigs, rabbits and rats intermittently to oxides of nitrogen. They reported that they produced a condition similar to centrilobular emphysema found in man.

Thurlbeck and Foley (113), in 1963, injected intratracheally cadmium chloride into guinea pigs. They found that one injection caused haemorrahage, edema and focal overdistension of air spaces. After multiple injections the lungs became condensed into scar around which were distortion and dilatation air spaces occurred. Scar emphysema was produced.

In 1964, Boren (14), exposed mice to carbon dust which had absorbed oxides of nitrogen. Partial damage to the alveolar walls and increase in alveolar size were produced without evidence of inflamation.

In a preliminary report, Gross et al (48), 1964, described the production of emphysema in silicotic rats by means of repeated intratracheal injections with papain. From further experiments (49), they found that a pure centrilobular lesion was demonstrable within six hours after the papain injection into normal rats. Panlobular emphysema was also found in rats which had received a larger dosage of papain or survived longer. They noted that the occurrence of an alveolar destruction was found without an associated inflammatory reaction.

Clay and Rossing (23), in 1964 , repeatedly exposed twenty-five dogs to phosgene. From the histological examination, pulmonary emphysema was claimed to have been produced in the dogs.

Hernandez et al (58), in 1966 , reported their microscopic observation that cigarette smoke in a highly concentrated form could produce parenchymal disruption in experimental dogs, especially in those subjected to smoke for prolong periods, i.e. more than a year. They noted that the lesion were related to an inflammatory component and closely resembled the lesion found in human emphysema.

Auerbach et al (5), in 1967 , reported that pulmonary fibrosis and emphysema were produced in their experimental dogs exposed daily to cigarette smoke. The lesions were similar to those observed emphysema in humans.

Blenkinsopp (13), in 1968, studied the pathogenesis of emphysema in rat lungs by the production of various types of lung damage and dust foci. He found that emphysema followed acute bronchiolo-alveolitis due to the intrabronchial injection of papain and rarely followed bronchiolar scarring.

Anatomy of Normal Lung

For a reasonably clear picture of the disease, a short review of normal lung structure that plays a major part in determining function, which is an important feature of emphysema, will be given below.

The lungs of dogs bear a marked structural similarity to human lungs (64). The trachea divides into right and left main bronchi, each bronchus dividing dichotomously many times and eventually ending blindly in alveolar sacs. The conducting airways consist of bronchi and bronchioles which are distinguished from each other by the presence of cartilage in the walls of the former. The carilages of the main-stem bronchi and the lower lobe bronchi are horseshoe shaped as in the trachea, and presumably are responsible for maintaining patency of the bronchi. The cartilages are less complete, consist of irregular plates, as the pathway proceeds distally. The bronchial muscle lies between the ends of the cartileges and finally they encircle the bronchi. The epithelium of the bronchi is of the pseudostratified ciliated type and contains numerous globlet cells. The epithelium is progressively thinner and decreased in globlet cells as the pathways proceed distally. Bronchioles of the first order arising at the tip of the terminal bronchus continue branching to produce three or four further divisions that are fully lined by

cuboidal epithelium. The last to be so lined is called a terminal bronchiole, in which the goblet cells and cilia have disappeared. The remaining part of the lung is concerned with both conduction and gas exchange. These are respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli, all of which are often referred to as the "acinus". Classically, three orders of respiratory bronchioles succeed the terminal bronchiole. Respiratory bronchioles are partly alveolated with the rest of their wall lined by cuboidal epithelium. More alveoli appear in the walls of succeeding generations of respiratory bronchioles, and the wall of a third order respiratory bronchiole is largely formed by alveoli. Immediately beyond the respiratory bronchiole lies the alveolar duct which is entirely alveolated with smooth muscle in its walls at the opening of the alveoli. Several alveolar sacs are formed at the distal end of alveolar ducts. They are the blind ends of respiratory pathways and are entirely alveolated, but these alveoli have no smooth muscle at their openings. Adjacent alveoli are separated by two layers of ultra thin alveolar epithelium and a little connective tissue containing capillaries, together with elastic tissue and reticulin fibrils. However, these walls are incomplete, there being small defects or alveolar pores (Cohn) by which adjacent alveoli and air passages communicate. These pores are located in some of the interspaces of the alveolar capillaries and normally are too small to be demonstrated well in routine histological sections.

Elastic Framework.

Elastic fibers are found throughout the lung. In the tracheo-bronchial tree, elastic fibers are partially concentrated in the membranous sheet incorporating the cartilaginous elements. In the bronchioles, the elastic fibers are arranged in an outer, longitudinally oriented layer which grades over into a layer of mixed longitudinal, oblique, and circular fibers. The outer longitudinal fibers intermingle with elastic, collagenous, and reticular fibers in the wall of adjacent alveoli. The arrangement of elastic fibers in the alveolar ducts and their surrounding alveoli is complex. There are two types of elastic fibers: circulatory fibers along the vascular wall, and respiratory fibers encircling and supporting alveolar entrances, preventing over-distension of the alveolar opening. Some fibers traverse interalveolar septa.

PATHOLOGY OF EMPHYSEMA

Definition.

There is now general agreement that pulmonary emphysema is best defined as a structural disorder. Two such definitions of emphysema are available and each has its respective advantages and defects. The Ciba Symposium (40) defined emphysema as "a condition of the lung characterized by increase beyond the normal in the size of airspaces distal to the terminal bronchiole, either from dilatation

or destruction of their walls". Both the American Thoracic Society (2) and the World Health Organization (29) limited the use of the term emphysema to enlargement of these airspaces accompanied by destructive changes. The part thus affected is the acinus. Increase in the size of the acinus beyond normal without destruction is termed "overinflation" and not emphysema. The advantage of the latter definition is that the destructive changes are usually easily recognized, and to a great extent are independent of minor differences in the degree of inflation of the lung. The disadvantage is that it displaced well known terms such as compensatory emphysema and it does not define destruction. However, in the present study the latter definition is preferred.

Classification

A variety of types of emphysema have been defined and described (40, 101, 115). It is difficult to make a satisfactory classification of all examples of emphysema rigidly into one or another type. There are considerable expert differences of opinion. However, in relation to the present study, the fundamental different anatomical types will be described. It is best classified in relation to the nature of involvement of the acinus.

Centrilobular Emphysema

Gough (47) described this type in 1952 and he amplified this with Leopold (67) 5 years later. In this type of emphysema, the respiratory

bronchioles are selectively or predominantly affected. The destroyed and enlarged respiratory bronchioles tend to become confluent both in series and in parallel and thus form emphysematous spaces. The alveolar ducts, alveolar sacs, and alveoli which are situated distal to the emphysematous spaces are often preserved. Hence, in a classical case the picture is one of neatly punched out holes separated by relatively normal appearing alveolated structures. The disease is more common and usually more severe in the upper zones of the lungs (the upper lobe and the superior segment of the lower) (114). The walls of the spaces and/or the supplying bronchioles (i.e. respiratory bronchioles to the emphysematous spaces) usually show histological changes of chronic inflammation and are characteristically pigmented. Loss of elastic and muscle fibers are frequent findings. The supplying bronchioles are quite often narrowed but may be normal (67). It is generally associated with chronic bronchitis when the disease becomes more severe, and it is difficult to appreciate the centrilobular origins of the disease. In this case, it is advisable to examine the areas least severely diseased in order to identify that the emphysema originated in a centrilobular position. Bronchographic study of centrilobular emphysematous lung may show the control material has outlined the emphysematous spaces leading to peripheral pooling (56,68).

Panlobular Emphysema

This form of emphysema is characterized by a more or less uniform enlargement and destruction of the acinus. The respiratory bronchioles are not selectively affected as they are in centrilobular emphysema. In the earliest stage of panlobular emphysema there is a loss of the normal pulmonary architecture with effacement of the sharp distinction of size and shape between ducts and alveoli. These changes result in a coarsening of the honeycomb structure of the lung. There is marked variation in the calibre of the fenestrated opening (129). The elastic tissue appears to be thickened nearest the ductal mouth with disappearance of the elastic and the reticular fibers from the bases of alveolar sacs. As the disease progresses, there is gradual loss of all components of the acinus until only a few strands of tissue remain - a "cotton candy" appearance (115). The cut surface of the lung shows protrusion of the bronchi and blood vessels as the parenchyma falls away. The precise morphology in the earliest stage is still unclear. There is some suggestion that alveolar ducts may be particularly involved and that this form of emphysema be designated "alveolar duct" emphysema (114). Panlobular emphysema is more or less randomly scattered throughout the lung, with a tendency for more frequent occurrence in the lower and anterior zones of the lung. It becomes more severe in the lower zones of the lung (114). Panlobular emphysema may be found associated with chronic bronchitis (115). It is frequently associated with

deformities of the major bronchi which may cause obstruction to air flow (129). The bronchi in emphysematous areas often demonstrate cylindrical ectasia as seen in the bronchogram (129).

Irregular Emphysema (Paracicatrical Emphysema or Scar Emphysema)

This emphysema shows no particular localization within the acinus and the acinus is irregularly involved. Emphysema is most classically seen in relation to scarring. It forms a zone of emphysematous alveoli around a core of scar. If the scars are small and numerous, each being surrounded by a wide zone of emphysema, the lung gives the appearance of a massive emphysematous region. There is usually loss of capillaries in the alveolar wall. The alveoli may be so tenuous that little structure is recognizable.

Paraseptal or Periacinar Emphysema

This is a condition in which the periphery of the acinus is selectively involved. The alveolar regions which lie against connective tissue, around large bronchi and blood vessels, pleura and connective tissue septa, are affected. The sites commonly affected are the sharp edges such as the anterior edge of the upper or middle lobe and lingula and the costodiaphramatic rim (101). Paraseptal emphysema is generally associated with obviously increased collagen, and thus may be related to scarring.

The first two types are the most common and important forms of emphysema. About 50 percent of random necropsies show well defined centrilobular and/or panlobular emphysema (114).

THEORY AND PRINCIPLE OF METHODS

Lung Volume:

On agreement of American respiratory physiologists in 1950 (26), lung volumes are divided into four volumes and four capacities. The tidal volume (V_T) is the volume of gas inspired or expired during each respiratory cycle. The inspiratory reserve volume (IRV) is the volume that can be inspired from the end inspiratory position. The expiratory reserve volume (ERV) is the volume which can be expired by a maximal effort beginning at the position of resting expiration. The residual volume (RV) is the volume of air remaining in the lungs at the end of a maximal expiration. These four volumes make up the total lung capacity (TLC) which is the volume of air in the lungs after a maximal inspiration. V_T, IRV, and ERV make up the vital capacity (VC) which is the maximal volume of air expired after a maximal inspiration. The inspiratory capacity is the maximal volume of gas that can be inspired from the resting expiratory level and is the sum of V_T and IRV. The functional residual capacity, the sum of ERV and RV, is the volume of gas remaining in the lungs at the resting expiratory level.

Methods of Measurement:

The spirometer is commonly used in the measurement of lung volumes. Volume changes, during respiration, are the volume of gas entering and displaced out of airways and the other part due to compression of gas within the lungs. The latter is neglected if the volume changes

are measured by a spirometer. In most circumstances this is an unimportant distinction but during forced breathing it may be very important. It is particularly important to know true lung volumes during forced expiration because the static recoil of the lungs which plays so important a role during forced expiration depends on true lung volume and not simply the volume displaced out of the mouth. Body plethysmographs (31, 83) are advantageous for measurement of volume changes since they take any gas compression into account.

Residual Volume and Functional Residual Capacity:
Thoracic Gas Volume:

RV and FRC are usually measured together. These two components of the lung volume cannot be measured by direct spirometry and must be determined by indirect means.

1. Plethysmographic Methods in Measuring Thoracic Gas Volume - FRC

Thoracic gas volume is defined as the volume of gas in the thorax, whether in free communication with the airways or not. DuBois et al (31) described their body plethysmograph method of which the principle of measurement is based on Boyle's Law, the statement of the relationship between changes in pressure and volume of a gas if its temperature remains constant. The volume of a gas varies inversely with the pressure to which it is subjected. The subject is completely enclosed in a rigid box,

breathing air through a mouth piece. At end-expiration, the alveolar pressure, P, is equal to the atmospheric pressure because there is no gas flow. V is the unknown volume of gas at the end of expiration. If the airway is then occluded so thatno pulmonary gas can escape when the subject makes a breathing motion against the block, the pulmonary gas is compressed and decompressed. This creates a new thoracic gas volume ($V + \Delta V$, where ΔV is the increase in volume caused by decompression) and a new pressure ($P + \Delta P$).

Then: $PV = (P + \Delta P)(V + \Delta V)$

In such a closed system, pressure at the mouth is considered to be the same as alveolar pressure if the glottis of the subject remains open. Hence, the change in pulmonary gas pressure can be measured during airway occlusion by a gauge in the airway on the pulmonary side of the closed shutter. The increase in thoracic gas volume (ΔV) is determined by noting the rise in plethysmographic pressure which is detected by a very sensitive electric gauge (31) or it can be measured directly by a volume displacement body plethysmograph (83). Knowing P, ΔP, and ΔV, the equation of Boyle's Law can be solved for the unknown original thoracic gas volume, V. In this circumstance, if one occludes the airway at the end of a normal expiration, which is usually used because this level is more constant than the others, the thoracic gas volume is the functional residual capacity.

2 . Air Dilution Methods:

The principle of the methods depends on the analysis of insoluble gases; that is gases that do not leave the alveolar gas readily

to dissolve in blood or lung tissue.

2A. The Open Circuit Technique

This method is based on the determination of the amount of N_2 diluted in the lung. When the subject is breathing air which contains about 80% N_2, this amount of nitrogen will be diluted in the lungs. The amount of nitrogen in the lungs can be measured by having the subject inspire 100% O_2 (N_2 free) and then washing the N_2 out of the lungs into a spirometer (previously flushed with O_2 so that it is N_2 free) for generally 7 minutes. The N_2 concentration in the expired gas can be measured and the total amount of N_2 which comes from the lungs can be computed if the expired gas is known. Since this amount of N_2 represents 80% N_2 in the lungs, then the total alveolar gas volume, at the moment that the N_2 wash out began, can be calculated.

2B. Closed Circuit Technique

The principle is the same as that used in the open circuit technique but Helium (He) is usually used as the test gas. The subject is made to breathe gas containing He from a container in the closed circuit system, until mixing is complete; that is, when the concentration of He becomes the same in both the lungs and the container. If the initial

volume of gas and the concentration of He are known, the initial volume of gas in the lungs can be calculated from the amount of He that has been diluted by the alveolar gas.

Thoracic gas volume, FRC, measured by the plethysmograph is the same as FRC measured by the dilution method in healthy individuals who have no poorly or non-ventilated areas (31). However, it exceeds FRC measured by gas dilution in some patients who have non-ventilated lung spaces (103). Thoracic gas volume measured by the plethysmographic method provides a more valid picture of the lung volume in many patients with emphysema. The dilution method can be used to obtain more accurate results if the test period is prolonged (105).

Other subdivisions of lung volume can be measured directly on a simple spirometer, from the recording of tidal excursions followed by a maximal inspiration and then a maximal expiration. By this means, VC, V_T, IRV, ERV are made available on the record. In this test, no time limit is imposed. RV can be obtained from the difference between FRC and ERV. TLC is the sum of FRC and IC.

Since lung volume varies with temperature and pressure changes, it is generally agreed that all lung volumes and ventilatory volumes should properly be corrected to body temperature and ambient pressure saturated with water (BTPS). Only under these conditions do they reflect the actual volume excursions of the lungs and chest wall (15).

Measurement of Diffusing Capacity of the Lung:

An important process relating to O_2 and CO_2 exchanges in the lung is the physical diffusion of the gases across alveolar-capillary membranes from a high partial pressure to a lower partial pressure.

In order to test this physiologic diffusion it requires the use of a gas which is considerably more soluble in blood than in the alveolar capillary membranes. There are only two such gases available, O_2 and CO. The measurement of the quantity of O_2 or CO moving from alveolar gas into pulmonary capillaries is defined as "diffusing capacity". It is the milliliters of gas STPD per minute per mm. Hg of partial pressure difference between the alveolar air and the pulmonary capillary blood diffused across the pulmonary membrane (26).

When O_2 or CO diffuses from the alveoli into capillaries they must pass across a surface film covering the alveolar lining, the alveolar membrane, the interstitial fluid and a capillary endothelium; then diffuse in the plasma until it reaches a red blood cell and traverses its membrane to combine chemically with Hb molecules. The rate of movement of the gas across membranes depends on the partial pressure gradient of the gas in the alveoli and in the plasma, the thickness of the pathways and the surface area for diffusion. These are the factors influencing diffusing capacity.

The exchange of O_2 is of more intrinsic importance than CO but the O_2 method for measuring diffusing capacity is more difficult and time consuming (27). Therefore, it has been largely replaced by the CO methods.

Carbon Monoxide Methods for Measuring Pulmonary Diffusing Capacity (D_{Lco}):

Carbon monoxide is ideally suited for the measurement of the diffusing capacity of the lung because it has affinity for Hb 210 times greater than that of O_2 (27).

Hence, because of this affinity all the CO that crosses the pulmonary membrane at a very low alveolar CO tension is bound. Also, the effect of a local back pressure of CO, built up in the layer of plasma, causing a reduced rate of transfer from alveolar gas into plasma, can be avoided. The Hb components for CO are so large that they can combine with all the CO molecules that diffuse from the alveolar gas to the capillary blood at low alveolar CO tension. Therefore, the transfer of CO is not limited by the rate of pulmonary blood flow (except in the presence of severe anemia) and the capillary CO tension can be assumed to be equal to zero. From the definition, the pulmonary diffusing capacity for CO is:

$$D_{Lco} = \frac{\text{CO uptake in ml/min.}}{\text{mean alveolar } P_{co} \text{ in mm Hg} - \text{mean capillary } P_{co} \text{ in mm Hg.}}$$

$$\text{mean capillary } P_{co} = 0$$

$$\text{hence} \quad D_{Lco} = \frac{\text{CO uptake in ml/min.}}{\text{mean alveolar } P_{co} \text{ in mm Hg.}}$$

The CO uptake can be measured by the two following techniques:

1. Breath Holding Method:

The original method was published by Kroghs (65) and was modified

later by Ogilvie and his colleagues (89). It has come to be known as the modified Krogh method. In this method the subject inspires maximally from residual volume a gas mixture containing a low concentration of carbon monoxide and helium, holds his breath for a measured time and then rapidly expires an alveolar gas sample. It is assumed that He and CO are distributed similarly after a single breath. The initial alveolar CO concentration in the expired alveolar sample can be calculated from an equation:

$$F_{Aco} = F_{Ico} \times \frac{\text{He\% in expired alveolar sample}}{\text{Inspired helium percentage}}$$

Knowing the change in CO concentration in the alveolar sample during the period of breath holding, D_{Lco} can be calculated from Krogh's equation:

$$D_{Lco} = \frac{\text{Alveolar volume (STPD)} \times 60}{\text{Time (seconds)} \times (\text{barometric pressure}-47)} \times \text{Natural log}\left[\frac{F_{Aco}'}{F_{Aco}''}\right]$$

F_{Ico} = inspired CO concentration

F_{Aco}' = initial CO concentration in the expired alveolar sample

F_{Aco}'' = final CO concentration in the expired alveolar sample

The advantage of this method is that it is a quick test, requires little co-operation from the subject and no blood samples are needed.

However, the measurement is not that of a normal physiological breathing, and dhyspneic subjects would find it difficult to hold their breath.

2. Steady-State Method:

In all the steady-state methods the CO uptake is measured in essentially the same manner; that is, as the difference between the total volume of CO inspired (inspired concentration x inspired minute volume) and that expired (expired concentration x expired minute volume). The subject breathes a mixture containing a low concentration of CO (about 0.1 - 0.2%) for about a minute, by which time the CO exchange has reached a steady state; i.e. the alveolar P_{co} reaches a plateau, and the measurements are made.

The differences among the techniques lie in the method of estimating alveolar P_{co} (10, 15). The Filley and the end tidal methods are widely used and hence the principle of these techniques will be given here.

(a) Filley Method - Alveolar CO Calculated From Measured Arterial Pco_2

In this method, expired gas is analyzed for CO_2 in addition to CO and arterial CO_2 tension is measured simultaneously. Filley et al (38) the originators of this method assumed that arterial Pco_2 equals mean alveolar Pco_2. The mean alveolar CO could be computed from the following relationship:

$$P_{Aco} = (P_B - 47) \frac{F_{Eco} - rF_{Ico}}{I - r}$$

$$r = \frac{P_{aco_2} - P_{Eco_2}}{P_{aco_2}}$$

P_{Aco} = mean alveolar CO tension

P_B = barometric pressure

F_{Ico} = inspired CO concentration

F_{Eco} = expired CO concentration

P_{aco_2} = arterial CO_2 tension

P_{Eco_2} = mix expired CO_2 tension

This technique is extremely sensitive to slight errors in the analysis of CO_2 and CO which can lead to larger errors in estimations of the diffusing capacity. It is also affected by changes in the pattern of breathing. In exercise, the error would be less than half of that amount. However, this technique has been widely and successfully used in clinical disorders (10).

(b) Measurement of End Tidal CO Concentration:

In this technique, the end-expiratory CO value is considered equal to mean alveolar CO concentration. The sample, which is the last portion of expiratory gas, can be obtained by a Rahn sampler (99) or a timing device such as that used by Bates et al (8). It has been shown

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that end tidal sampling is a reliable estimation of resting diffusing capacity (8). However, the measurement of the resting steady-state end tidal method may, on occasion, be falsely lowered by a small tidal volume which fails to clear the respiratory and instrumental dead space (9). Bates (10) suggested that the fractional CO uptake should be calculated at the same time as the D_{Lco} is measured by this technique, since errors due to a low tidal volume are thereby made more obvious. This fraction gives an estimate of the normality or otherwise of CO uptake independently of any value found for the CO in the end tidal sample. The fractional CO uptake may be calculated from this expression:

$$\text{Fractional CO uptake} = \frac{F_{Ico} - F_{Eco}}{F_{Ico}}$$

which may be left as a fraction or multiplied by 100 and expressed as a percentage.

The steady state method has the disadvantage that diffusing capacity is affected by disorders in gas distribution (27). However, it has been found that it gives a much reduced diffusing capacity in patients with emphysema who, by the single breathing method give normal results (4). This method can be used to distinguish between emphysematous patients and bronchitics (9).

Mechanical Properties of the Lung:

Measurement of Elastic Properties of the Lung:

It has been pointed out that the ability of lungs to collapse when the chest is opened is due to their own retractive forces (elastic forces) (84). The most important factors effective on the retractive force of the lung are elastic tissue fiber and the surface force from the gas tissue interface. Other factors which may influence the elastic behaviour of the lung are tissue cells, smooth muscle, and pulmonary blood volume. It appears likely that the mechanical properties of these factors play little part in the elasticity of adult lungs (98). The elastic force increases with increasing lung volume and this property can be demonstrated by relating applied pressure and volume changes in a static condition. The slope of the line that results from plotting pressures against volumes serves as a measurement of the recoil properties of the lungs. The volume change per unit pressure change is termed the "compliance" and its unit is litre/cm H_2O. In normal subjects the pressure volume curve during a respiratory cycle shows a hysteresis loop* (84, 98).

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*The term "Hysteresis" is the failure of a system to follow identical paths of response upon application of and withdrawal of a forcing agent. The result of this failure to retrace the same path on withdrawal as on application is the formation of a hysteresis loop.

Lung Compliance Measurement:

Transpulmonary pressure developed during a no flow or static condition is equal to the recoil pressure of the lung alone (all pressures related to flow are zero) which is the pressure difference between that of the alveolar gas, P_{alv} and that at the pleural surface, P_{pl}, when the volume is held constant. During no flow with an unobstructed airway, alveolar pressure is equal to mouth pressure or pressure at the airway opening. Therefore, alveolar pressure can be measured at the airway opening. Pleural pressure is obtained by the esophageal balloon technique which has been described (see page 38). In this way transpulmonary pressure which is related to recoil pressure can be computed.

As mentioned previously, the measurement of elastic recoil pressure has to be done under static conditions. For a reasonably static state, a pressure volume curve is usually constructed by relating slow volume changes and the associated pressure changes. It may also be measured under dynamic conditions by determining the pressure change at the points of maximum volume excursion when gas flow is zero. The compliance obtained in this way is named "Dynamic compliance". Since more factors will affect the attitude of compliance during the dynamic rather than during the static condition and since the former condition was not studied in this study, the theoretical basis will not be presented here.

Mead et al (80) have shown that pressure-volume curves obtained during inflation and deflation for small volume cycles (that is,

normal tidal volume) are nearly superimposed and static hysteresis is frequently not detectable. However, it shows greater hysteresis with larger volume changes. Whatever the linear and reversible behaviour of a pressure volume curve for small volume changes it is in fact quite variable. It can change at the same volume depending on the state of the lung from which it is inflated, (11, 82). Bernstein (12) explained that the difference is influenced by the number of units of air spaces opened at the beginning of inflation. As the lung volume progressively increases, part of the alveoli are accompanied by further expansion and partly by the recruitment of new air spaces. During deflation, the air spaces remain open, the larger number of air spaces sharing a given volume. In these circumstances the stress on any unit of air spaces is smaller than during inflation (that is, the smaller pressure developed). Therefore, the deflation curve from any volume or pressure represents the true elastic behaviour of all those alveoli which have been inflated up to that volume or pressure while the inflation curve represents the combination of two processes, elastic expansion and recruitment of alveoli.

It has been pointed out, from the comparison of differences in the pressure volume characteristics of air filled and liquid filled lungs that surface tension operating at the gas-liquid interface within the lungs plays a significant role in the elasticity of mammalian lungs (84, 98). Surface tension arises from the cohesive forces between the molecules in and near an interface between dissimilar materials. When such a

tension exists in a concave surface, such as the alveoli, it generates a pressure difference across the surface which acts to reduce the volume contained within the surface as well as the area. For a given tension, the pressure difference becomes larger as the structure becomes smaller. However, the lung contains an alveolar lining substance to bring the tension down to a low value (24). By reduction of the lung volume or area, the molecular layer becomes more concentrated, and a force develops between the molecules, resisting compression. By this means, the interface force is modified, the lung is inflated with a high surface force and deflated with a surface force that falls to a lower value.

According to the above reasons, the compliance is usually measured from a pressure volume relationship on a deflation curve after maximum inflation within the tidal volume range. In this way, the effect of the recruitment of alveoli is eliminated and the surface force is minimized while the most reaction may be interpreted in terms of the tissue elastic property. All measurements should be done after inflation of the lung two or three times and then record static deflation pressure. This is a successful method to obtain consistent numbers from run to run and from time to time (85). For comparative measurements of static recoil pressures, it is of great importance to keep the same conditions of volume history for all measurements.

Tissue fibers that have elastic properties are collagen, elastin (elastic fiber) and reticulin. Robb-Smith (104) demonstrated that reticulin fibers which are widely distributed in the lungs are considered chemically similar to collagen. Therefore, it is reasonable

to include them as part of the collagen network. The mechanical significance of the fiber is unknown. Pierce, Hocutt, and Hefley (92) studied the tissue retractive force of saline filled lungs when the lungs had been treated with elastase to dissolve elastic fibers. They reported that elastin accounts for nearly all the tissue elastic behaviour, and that collagen acts principally as a supporting framework for the elastic network, limiting its range of extension to prevent rupture of the fiber elements. Hence, the changes in elastic behaviour of the lung, when measurement is performed by the method having been described, is principally reflected in the changes of the property of elastic fibers.

Measurement of Pulmonary Flow Resistance:

When pressure is applied to the lung it causes lung and air in motion. Applied pressure will be met by pressures developed in the lung. Newton's third law of motion states that "a force applied to a body is met by an equal opposing force developed by the body". Opposing forces developed by the body are of three sorts: (1) static forces, relating to the degree to which the system has been deformed; (2) frictional or resistive forces, relating to the rate at which the system is deformed; (3) inertial forces, relating to any acceleration taking place.

For the lung, deformation is measured in terms of volume change and force in terms of pressure change. Hence, applied pressure is equal to pressure developed in the lung; that is, the sum of the static

or elastic component, the frictional or flow resistive component and the inertial component of pressure. It can be rewritten in the following equation:

$$P_T = P_{el} + P_{res} + P_{in} \quad \ldots\ldots\ldots\ldots (1)$$

where P_T = transpulmonary pressure

P_{el} = static or elastic component of pressure developed by lung tissue

P_{res} = flow resistive or frictional component of pressure, related to the physical properties of gas and the flow geometry of the airways and tissue flow resistance.

P_{in} = inertial pressure related to gas and tissue in acceleration.

Inertial pressure (P_{in}) is normally small and insignificant under physiologic conditions (84). Therefore, the equation becomes:

$$P_T = P_{el} + P_{res} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Pulmonary resistance measured in $cmH_2O/L/sec.$ can be obtained

from measurements of flow resistive pressure and simultaneous flow. Flow can be measured by means of a pneumotachograph (46). From equation 2, the flow resistive component of pressure can be solved if the elastic component of pressure is subtracted.

$$P_{res} = P_T - P_{el} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Since transpulmonary pressure is measured as the pressure difference between the airway opening or mouth pressure and intrapleural pressures and if pressure related to the lung static recoil (P_{el}) is subtracted from the latter, the resistive component of pressure is the result. Then pulmonary resistance can be computed.

There are many ways to separate the elastic and resistive components of pressure. It may be estimated from known static volume-pressure measurements and subtracted. The method was first undertaken by Neergaard and Wirz (121) who reported that the elasticity of the lung could be measured at the points where the velocity of air movement was zero, i.e. at the end of respiration. Under this condition only elastic pressure appeared. Therefore, a record of intrapleural pressure and simultaneous airflow at tidal volume range permits a measure of lung elasticity and the resistance to movement. This measurement was made on the assumption that the linearity and reversibility of elastic pressure

established for small, slow volume changes are not influenced when the volume changes are produced more rapidly.

Mead and Whittenberger (78) subtracted elastic recoil pressure by electrical means. By this technique, a cathode ray oscilloscope is used as a coordinate plotting device. Flow is displayed on the Y axis and transpulmonary pressure (P_T) on the X axis. A closed loop is obtained on the oscilloscope screen during a single respiration. The distance along the X-axis between the points of intersection is equal to P_{el}. Since P_{el} varies directly with volume change, a voltage proportional to volume change is then impressed on the X-axis plates to subtract from the transpulmonary pressure voltage. The volume voltage is gradually increased and subtraction is complete when the loop is closed. Pulmonary resistance can be obtained from the slope.

The second method used to separate the recoil and resistive pressures involves the production of a sudden mechanical interruption of the air stream. Assuming that the volume of the lung does not change during closure of the airway opening, the pressure difference between the airway and the pleural surface changes abruptly by an amount equal to the flow resistive pressure existing at the instant of interruption.

Hence, the form of the equation becomes:

$$\text{Before interruption } P_{T_1} = P_{el} + P_{res}$$

After interruption $P_{T_2} = P_{el}$ (P_{res} is zero during no flow)

Thus $P_{res} = P_{T_1} - P_{T_2}$

This method was first used by Vuilleumier (123) and has been extensively applied by Fry et al (45). It has the advantage of not being influenced by the shape of the volume-elastic pressure function or the degree of static hysteresis.

DuBois et al (32) have introduced the force oscillation technique for estimating total respiratory flow resistance. The lungs are oscillated with a sine wave of air flow at their resonant frequency. At this frequency, the pressure required to overcome inertia cancels that required to overcome elastic recoil. Therefore, during the induced cycle the lung will be dependent upon the flow resistance. The method is of potential value in the study of resistance to breathing of anesthetized or unconscious subjects (39).

Method of Measuring Intrapleural Pressure

As mentioned previously, transpulmonary pressure is the pressure difference between mouth pressure and intrapleural pressure. Mouth pressure is measured by means of a side tap on the breathing tube

and intrapleural pressure can be obtained by introducing a needle or catheter into the pleural space. Direct measurement of intrapleural pressure is impractical, because there is a risk of producing air embolism or pneumothorax. The measurement of intraesophageal pressure has been introduced as a means to estimate intrapleural pressure. Direct comparative studies from the simultaneous recording of intraesophageal and intrapleural pressures have shown that the esophageal pressure reflects the intrapleural pressure rather closely (44, 81). The intraesophageal pressure is usually a few centimeters of water higher than a simultaneously measured intrapleural pressure. The most widely used system for transmission of esophageal pressure employs an air filled latex balloon sealed over a polyethylene catheter placed in the esophagus. The balloon transmits pressure to a manometer. Although the balloon can reflect the intrapleural pressure, the accuracy of transmission also depends on many factors. The volume of gas, the size and the position of the balloon in the esophagus, as well as body posture have to be taken into account.

The distortion in the measurement of pressure increases with balloon volume, especially at both extremes of the vital capacity. Milic-Emili et al (86) found that a close approximation of the extrapolated pressures was obtained with very small balloon volumes. The site of the balloon in the lower two-thirds of the esophagus accurately reflects

intrapleural pressure while the upper part shows a big variation (87). In order to avoid this artifact in the upper part of the esophagus a shorter balloon is preferably used. Balloons of 5 to 10 cm long yield a result closely related to intrapleural pressure (87).

The esophagus may be influenced by nearby structures: that is, the body position may affect the transmission of pressure in the esophagus. The esophageal pressure is relatively more positive in the supine than in other postures because of the weight of structures anterior to the esophagus. However, in subjects seated upright the recorded pressure in the esophagus agrees well with that recorded in the pleural space (37, 81). Further studies by Milic Emili et al, revealed that large artifacts with postural changes are absent when the pressure is recorded in the middle part of the esophagus. If the influencing factors are avoided or minimized in performing intraesophageal pressure measurements, the pressure changes in the esophagus are reliable indices of intrapleural pressure changes in respiratory mechanics studies.

Measurement of Central and Peripheral Airway Resistance

In order to locate the airway obstruction in emphysema, methods of bronchial pressure measurements have been used. The use of bronchial catheters to record simultaneous pressure in the main stem

bronchi and segmented bronchi was found to produce sources of error (73).

Macklem and Mead (75) recently developed a new technique in partitioning the lower airway resistance which overcomes the technical obstacles of previous experiments of the past. They described an ingenious approach to the measurement of central and peripheral airway resistance by using a retrograde catheter. The catheter measuring the pressure in an airway of approximately 2 mm. in diameter is a piece of polyethylene tubing which is bell shaped at one end. It is passed through the trachea but instead of extending out of the trachea and thereby obstructing the airway in which it is measuring pressure, it extends peripheraly in a retrograde fashion through the parenchyma and pleural surface until the bell is wedged in a bronchus, leaving the airway central to it completely unobstructed.

It is assumed that the pressure in a single bronchus represents the pressure in all other bronchi in the lung of a similar size. It is possible to measure the resistance of airways between the retrograde catheter tip and the alveoli, the peripheral resistance (R_p) and the other component between the retrograde catheter and the trachea, the central resistance (R_c). The R_p was obtained by measuring the pressure difference between bronchial pressure (P_{br}) and alveolar pressure, i.e. pleural pressure (P_{pl}), when the pressure due to elastic recoil is electrically subtracted from the latter and related to the

flow at the trachea: $R_p = \frac{P_{br} - P_{pl}}{\dot{V}}$. The resistance of the airway central to the catheter (R_c) can be similarly obtained from the pressure difference between bronchial pressure and tracheal pressure (P_{tr}) and this difference then divided by the related flow: $R_c = \frac{T_{tr} - P_{br}}{\dot{V}}$

The inertial component at the resonant frequency used can be eliminated graphically by varying the amplitude of the speaker cone deflection and measuring the pressures and flows only at points of peak flow when acceleration is zero. The other method employs an electrical subtraction of the inertial component from the pressures measuring a signal proportional to the acceleration. The electrical method appeared to be more satisfactory. The accuracy of this method in partitioning airway resistance has been supported by the latter work (56).

Measurements of Emphysema

Preparation of Lung for Quantitative Studies

There is no method of quantitative or even roughly evaluating emphysema at autopsy which is valid without prior inflation and fixation of the lung. The "Report of the Committee on Preparation of Human Lungs for Macroscopic and Microscopic Study" (102) earlier recommended inflation of the lungs through the trachea or bronchus with a 10% formalin solution, buffered with 5% sodium acetate, under a pressure of 8 to 12 inches or 20 to 30 cm of water, until the normal

contours of the inflated lungs were re-established. Since then the method of inflation-fixation with formalin has been used by many investigators in the field. Simplifications and modifications have also been made. A recent study of the methods used indicated that a modification of Heard's liquid formalin method is probably the best standard procedure for wide application (109). The lungs are inflated intratracheally with liquid formalin at a constant transpulmonary pressure of 25 to 30 cm of water while the lungs float in a large volume of fixation for a period of 48 to 72 hours.

For macroscopic examination the lungs are cut sagitally(after inflation-fixation) into 1 cm thick slices. The translucency of the lung can be overcome by a simple method of impregnating wet slices of the lung with a precipitate of barium sulphate (52) (barium chloride soaking followed by sodium sulphate) to obtain better contrast and thereby detect lesions.

Sampling of the Lung

On any histoligical analysis of the lung it is important that the selection of samples of the lung give a picture of the whole organ. There are two methods available:

1. Systematic Sampling: This method involves taking blocks of tissue at given intervals throughout the lung. The disadvantage of the method

is that, if the diseased areas have a similar type of arrangement to the sampling pattern, the sample will be unrepresentative of the lung as a whole.

2. Random Sampling: The tissue blocks are selected by means of a random number table (35). This method has the property of securing a small group of blocks of tissue possessing the same characteristics as the entire lung. By this means, since the sample units have an equal chance of selection, a highly unrepresentative selection is possible.

To prevent the occurrence of this type of selection, a compromise between random and systematic sampling is used. This is the stratified random sampling method.

Methods of Measurement

1. Subjective Methods

The gross appearance of the lungs is examined with the naked eye or through a stereomicroscope.

(a) Measurements of Extent Alone. The lungs are divided into zones from as little as two zones (upper and lower lobes), then multiple 1 cm area as defined by an overlying grid to points (118). The impregnated slices of lungs are then examined under water for the amount of emphysema. The extent of emphysema is the percentage involvement

of the lung parenchyma by emphysema. The disadvantages of these methods are that no distinction is made between 100 per cent involvement by mild and by severe panlobular emphysema. The different lesions are not distinguishable. Furthermore, the measurements may be affected by the subjectiveness of the observer. A judgement must be made at each area for the lesion.

However, Dunnill's point counting method is the least subjective of all methods (35). This method is based on the principle that the proportionate volume of one area to another is the same as the proportion of random points contained in each area. The measurement can be done by placing the point counting grid over the lung slices. On the grid, the points lie 1 cm apart and are situated at the angles of equilateral triangles with 1 cm sides. (This distance of separation has been found to give good precision and reproducibility on the emphysematous lung). Since one cannot see through an opaque finite point on the grid, the modifications made of Dunnill's method (117) have been to replace dots with holes in the grid. The sheet and lung slices are examined under water with the naked eye using a hand lens or a dissecting microscope. The latter is a more sensitive method in recognizing mild grades of emphysema. The tissue under each point or hole is categorized as non-parenchyma, normal parenchyma or emphysema.

If the three components to be measured occupy fractions P, Q, and R of the total volume V, the numbers of points p, q, and r

counted in these fractions will be in the same relation to each other as are the volumes, i.e.

$$p : q : r : \quad P : Q : R :$$

$$P + Q + R = 100\% = V$$

Of the total volume of the fixed lung is known, then the volume occupied by various components can be calculated.

By this method the more points assessed, the greater the accuracy of the method. It is advisable to express emphysema as a percentage of the lung parenchyma because the amount of non-parenchyma varies from slice to slice (118).

(b) Measurements of Extent Plus Severity. According to a Ciba Symposium (40), it was suggested that grading should be based on an estimate of the average severity with each lobe. In cases of focal and centrilobular emphysema, assessment of the severity should be based chiefly on the amount of respiratory tissue affected by emphysema. "Mild", "moderate" and "severe" grades represent less than 25 per cent, 25 to 50 per cent, and more than 50 per cent involvement of the respiratory tissue, respectively. In panlobular emphysema, the size of the air spaces is the main consideration in grading, which can be done by comparing the lesions with standard grading pictures.

Another method is derived from the Ciba Symposium (12) in which the average severity is assessed in ten zones (114). The average grade of severity in each zone was graded 0 to 3, i.e. "absent", "moderate" and "severe". Emphysema in the lung can be expressed as an average per zone, or a total of a maximum of 30.

The advantage of this method is that the extent as well as the severity of emphysema is measured. The disadvantage lies in the arbitrary scale of units and their subjectivity.

2. Measurement of Internal Surface Area

Since the method of measuring the internal surface area or air tissue interface of the lung is based on the fact that emphysema is a process of enlargement and destruction of the alveolated portion of the lung, the surface area of the alveoli (internal surface area) might be expected to reflect the extent and severity of emphysema. This measurement may be regarded as an objective method.

The theoretical basis is that in a convex three dimentional structure the average linear intercept is equal to four times the volume divided by the surface area, SA: $(Lm = \frac{4V}{SA})$. Hence, the internal surface area (ISA) of the lung can be calculated by the following formula:

$$ISA = 4V/Lm$$

where V = the volume of lung parenchyma

Lm = the mean linear intercept which is the average distance between alveolated surfaces.

The mean linear intercept is determined by placing a line randomly on histologic sections of the lung under a microscope, and the number of intersections of the line with interalveolar septa is then counted. The total distance (the length of the line multiplied by the number of times the line is placed on the lung sections) divided by the number of alveolar intercepts gives the mean linear intercept of processed tissue, i.e.

$$Lm = \frac{N\,L}{m}$$

where m = the sum of all the intercepts

L = the length of the traverses

N = the number of times the traverses are placed on the lung.

Since the mean linear intercept calculated from histologic slides is that of processed tissue, it must be corrected for shrinkage and distortion produced by processing and cutting. This shrinkage factor can be determined by measuring the size of the blocks of tissue prior to processing which can be obtained by using templates producing blocks of a known size. The size of the cut processed section can be measured with a microscope using a stage micrometer.

Lm is measured in the two dimensions of known shrinkage, i.e. vertical and the horizontal to the plane of the microtome blade. The shrinkage factor is then calculated as the square roof of the product of the horizontal and vertical shrinkage factors.

The volume of lung parenchyma can be obtained from the total volume of lung (air + tissue) multiplied by the fraction of parenchyma as determined by the point count method (35).

Since the internal surface area varies with the degree of lung inflation in a given subject (124), the lung must be inflated to a comparable degree, such as at a constant pressure of 25 cm of formalin. The internal surface area at this distending pressure will be referred to as ISA.

There are assumptions made to overcome errors produced by the various inflation techniques. The assumption is that all structures are altered equally in dimension with changes in lung volume. Therefore the internal surface area would change to the two-third power. The internal surface area corrected to lung volume (V_n) would be related to the internal surface area of 25 cm of intrabronchial formalin.

$$ISA_c = ISA \left(\frac{Vn}{TLV}\right)^{2/3}$$

ISA = alveolar surface area at 25 cm of formalin distending pressure.

ISA_c = alveolar surface area corrected to given volume

Vn = a given volume

TLV = total lung volume

The internal surface area of a arbitrary total lung volume of 2 liters is:

$$ISA_2 = ISA \left(\frac{2}{TLV}\right)^{2/3}$$

PROCEDURE

The experiments were performed on mongrel dogs,weighing from 27 to 69 lbs. Prior to injecting the papain the dogs were anaesthetized with intravenous thiopenthal sodium (initial dose 10 mg/lb). Light anaesthesia was continued during the experimental period with intermittent intravenous doses of pentobarbital (50-100 mg), given at 30 to 60 minute intervals. The trachea was intubated with a wide bore rubber endotracheal tube of 9.0 mm. internal diameter (the same tube was used in all experiments). The endotracheal cuff was inflated to prevent air leaks. A thin latex esophageal balloon, 5 cm. long and 2.5 cm. in circumference, sealed over a polythylene catheter with multiple holes around the covered part was then placed in the lower esophagus to measure pressure. Mild continuous suction was used to remove debris from the esophagus near the balloon site. The dogs were then placed in a volume displacement body plethysmograph in the prone position with a rest to support the head. The esophageal balloon was re-adjusted and put in place by passing it into the stomach and withdrawing it slowly until the pressure recorded from the balloon became subatmospheric and no further decrease in end expiratory pressure was recorded. The esophageal catheter then was secured in place. It was attached by means of a three-way stopcock to one side of a Sanborn 267b pressure transducer. The esophageal balloon was evenly inflated with 5 ml of air and then the air was removed until 3.0 ml was left during the recording period.

Transpulmonary pressure was obtained by comparing mouth pressure to esophageal pressure on a Sanborn 267b transducer. Flow was measured at the endotracheal tube opening with a small NIL pneumotachograph and Sanborn 270 transducer. Pressure, volume, and flow signals were recorded on a 4 channel Sanborn recorder and on a Tektronix storage oscilloscope. Thoracic gas volume was measured, using the DuBois technique (31) by occluding the airway at FRC for a few seconds. During this occlusion the mouth pressure and volume change while the dog attempted to breath were displayed on the oscilloscope. The volume pressure slope (nearly linear) was read off on precalibrated scales and multiplied by the barometric pressure less the vapor tension of water at body temperature to obtain the volume of FRC. A complete pressure volume diagram was constructed by using positive pressure to inflate the lungs to TLC (transpulmonary pressure 30 cm H_2O) and then deflating the lungs to RV, using suction. TLC was calculated by adding the inspiratory capacity to the thoracic gas volume at FRC and the residual volume was calculated by subtracting the expiratory reserve volume from the thoracic gas volume at FRC. Vital capacity was measured directly from the Sanborn recording paper.

Static compliance was taken from a slope of the static volume pressure curve in tidal volume range, recorded after inflation of the lungs one or two times.

Pulmonary resistance was measured at various lung volumes. For this determination, the dog was connected through the pneumotachograph to a loud speaker enclosed in a pressurized box. The desired lung volume was reached by blowing air into the box and allowing it to leak through the speaker into the lungs. The lung was then held at this volume and the resistance was measured by activating the loud speaker with an oscillator powered by a sine wave generator and blowing air into and out of the lung. Flow, measured with the pneumotachograph was displayed on one axis of the oscilloscope and transpulmonary pressure was displayed on the other axis. Flow resistive pressure was obtained by electrically subtracting elastic recoil pressure from transpulmonary pressure using the method of Mead and Whittenberger (78). The resistance was obtained by reading the slope of the pressure flow curve on the oscilloscope or by dividing the flow resistive pressure signal by the flow volume signal obtained from the Sanborn recorder.

The measurement of arterial blood gases and diffusing capacity was preliminary studied during the spontaneous breathing of dogs lightly anaesthetized. It was found that the minute volume did not remain stable in each of the experimental states. It was therefore necessary to measure other dogs during controlled minute ventilation. The dogs were paralyzed with a single intravenous dose of succinylcholine chloride 0.5 mg/lb., supplementary doses of 8-20 mg

being given every 5-10 minutes or when the animals made spontaneous respiratory efforts. The dogs were ventilated with a respiratory pump (Harvard Apparatus Co.) at a breathing frequency of 16 counts/min. and the tidal volume was adjusted so that the arterial CO_2 tension fell between 30 and 40 mg. Hg. The minute volume for each of the experimental dogs was set at the same tidal volume and frequency of the control dogs.

Diffusing capacity for carbon monoxide was measured by the steady state, end tidal sample technique as described by Bates et al (9). The dogs breathed the inspired gas containing 0.123 - 0.148% carbon monoxide in air. The CO content was measured by means of an infrared analyser with accuracy to 0.001% CO. Arterial blood gas composition: pH,Pco_2 and Po_2 were measured by electrometer IL Model 113 pH/Gas Analyzer with an accuracy of $\pm$0.005 for pH $\pm$0.5 mm Hg for Pco_2 and 1% full scale Po_2. The Siggaard-Andersen monogram (108) was used to obtain plasma bicarbonate.

The arterial oxygen saturation was measured by using the reflectance oximetry technique (American Opt. Oximeter). It is accurate to within $\pm$2% saturation. The blood sample used in analysis was drawn from a femoral artery. The results obtained from all measurements were the average of duplicate readings.

After the above data was obtained, the dogs were allowed to wake up and return to their cages. Within the next few days after

they had recovered completely they were re-anaesthetized and papain was injected. In order to obtain different degrees of emphysema, the doses of papain were varied from 1 and 2 mg/lb body weight and given at varying periods of time (see Table I). At the same time they were placed on antibiotic therapy (Penstrep) to control infection. The initial study was repeated two weeks after the first papain injection (for the dogs which lived more than two weeks) and the dogs were sacrificed with intravenous nembutal sodium after the final study was completed, one to four weeks after injection.

The lungs were then removed carefully without damage to the pleura. The resistance of the central and peripheral airways were measured on the excised lungs using the technique of Macklem and Mead (75). A piece of polyethylene tubing, bell shaped at one end, was positioned in the following way. A large polyethelene catheter was inserted into the bronchial tree until it was wedged. A piece of piano wire was then passed into the wedged catheter and out through the parenchyma and pleural surface, then the wedged catheter was removed. The end of the retrograde catheter without the bell was securely attached to the tracheal extension of the wire. By pulling on the wire at the pleural surface, the retrograde catheter was pulled through the airway and parenchyma until the bell wedged in

the bronchus (the size of the bronchus, which the catheter wedged, was examined and measured at post-mortem). The lung was enclosed in a plethysmograph. The technique by which resistance was measured is shown in Fig. 2 . The principles of the measurement were the same as described above.

Post-mortem bronchography was done by the insufflation of finely particulate lead into the lungs (68). X-ray films were taken at five different distending pressures (0, 5, 10, 20 and 30 cm H_2O), from full inflation to zero pressure. The diameter of tracheas, right and left main bronchi and their segments, down to posterior basal segment were measured from the bronchograms using a dissecting microscope with a micrometer eye piece (Bausch & Lomb Optical Co.). The accuracy of the micrometer was within 0.01 mm.

The lungs were inflated and fixed with formalin (10% formaldehyde) run into the lung via the trachea. They were initially inflated with formalin by low gravity pressure (from a formalin bottle, placed on a shelf). The fluid was allowed to run in until the edges of the lung were rounded. The lungs were then placed in a formalin tank in which it can float freely. The tracheas were connected with a formalin stream at a constant pressure of 25 cm of water. After at least eighteen hours, the total lung volumes were measured by means of water displacement and then were cut, saggitally, into slices 1 cm

thick. The fraction of lung parenchyma was counted on barium sulphate impregnated slices using a modified technique (117) of Dunnill's stratified random point count (35). A rigid plastic sheet with a number of holes, 1 mm in diameter and 1 cm equidistant from each other, was placed on the lung slices (fig. 3) and were then floated under water. The lung parenchyma was examined under the dissecting microscope. The tissue underlying each hole was categorized as either non-parenchyma (tissue more than 1.1 mm. in diameter), parenchyma (normal tissue less than 1.1 mm. in diameter), or emphysema. If more than one type of tissue lay beneath a hole, then the type of tissue which occupied the greater portion of the hole was recorded. Non-parenchyma was excluded and emphysema was expressed as a percentage of lung parenchyma, i.e.

$$\% \text{ emphysema} = \frac{\text{emphysema}}{\text{emphysema + parenchyma}} \times 100$$

The mid or medial sagittal slice of the lung was used for a paper-mounted whole-lung section, using the Gough-Wentworth technique. The lateral slices of the lungs were floated under water, and a plastic sheet divided into numbered squares with holes drilled at their corners was placed over the lung. Using a table of random numbers, stratified random squares were chosen for sampling, and the cephalic side of the squares was marked with headless pins. The random squares were stratified so as

to use two squares of the upper lobe, one square of the middle or lingula lobe and two squares of the lower lobe. The selected squares were allowed to have touching corners, but not common sides. The plastic sheet was removed, leaving the pins in place and standard size of plastic templates were placed with their cephalic side parallel to the two pins, their left corner touching the left pin. Blocks of lung tissue were then cut to the templates size. Paraffin sections 7 μ thick were prepared from these blocks; mounted on glass slides and stained with hematoxylin and eosin. Elastic tissue was studied from 50 and 100 thick sections stained with Sheridan's resorcin-crystal violet. The mean linear intercept of processed tissue was measured on 7 μ thick section by passing a line randomly through the slides. Measurements were made at 20 stratified random points on each slide. At each point the number of alveolar intercepts was counted on a right-angled cross hair of known length at that particular magnification. The mean linear intercept of fixed tissue (Lm) was calculated from the shrinkage of the block from fixed to processed tissue. The internal surface area (ISA) was calculated from the formula 4V/Lm (see page 47). The internal surface area was corrected to an arbitrary lung volume of 2 litres (ISA_2).

TABLE I

Dosage Schedule

Dog No.	Weight (lb)	Sex	*Papain dose	Time of Injection	Total dose mg	Time from papain to sacrifice (days)
9	48	Male	1 mg/lb	1	48	7
10	49	Female	1 mg/lb	1	49	7
11	24	Female	2 mg/lb	1	48	7
13	27	Male	2 mg/lb	1	54	14
15	27	Male	2 mg/lb	1	54	14
16	69	Male	1 mg/lb	1	69	14
17	50	Male	1 mg/lb/wk	4	200	28
18	45	Male	1 mg/lb/wk	4	180	28
19	44	Male	1 mg/lb/wk	4	176	28
20	48	Male	1 mg/lb/wk	4	192	28

* from papaya latex crystallized, suspension in 0.05M sodium acetate, pH 4.5

1 mg will liberate approx. 4.0 moles NH_3/min.
form Benzoyl-L-arginine amide at pH 6.0 at 37°C
Sigma Chemical Company.

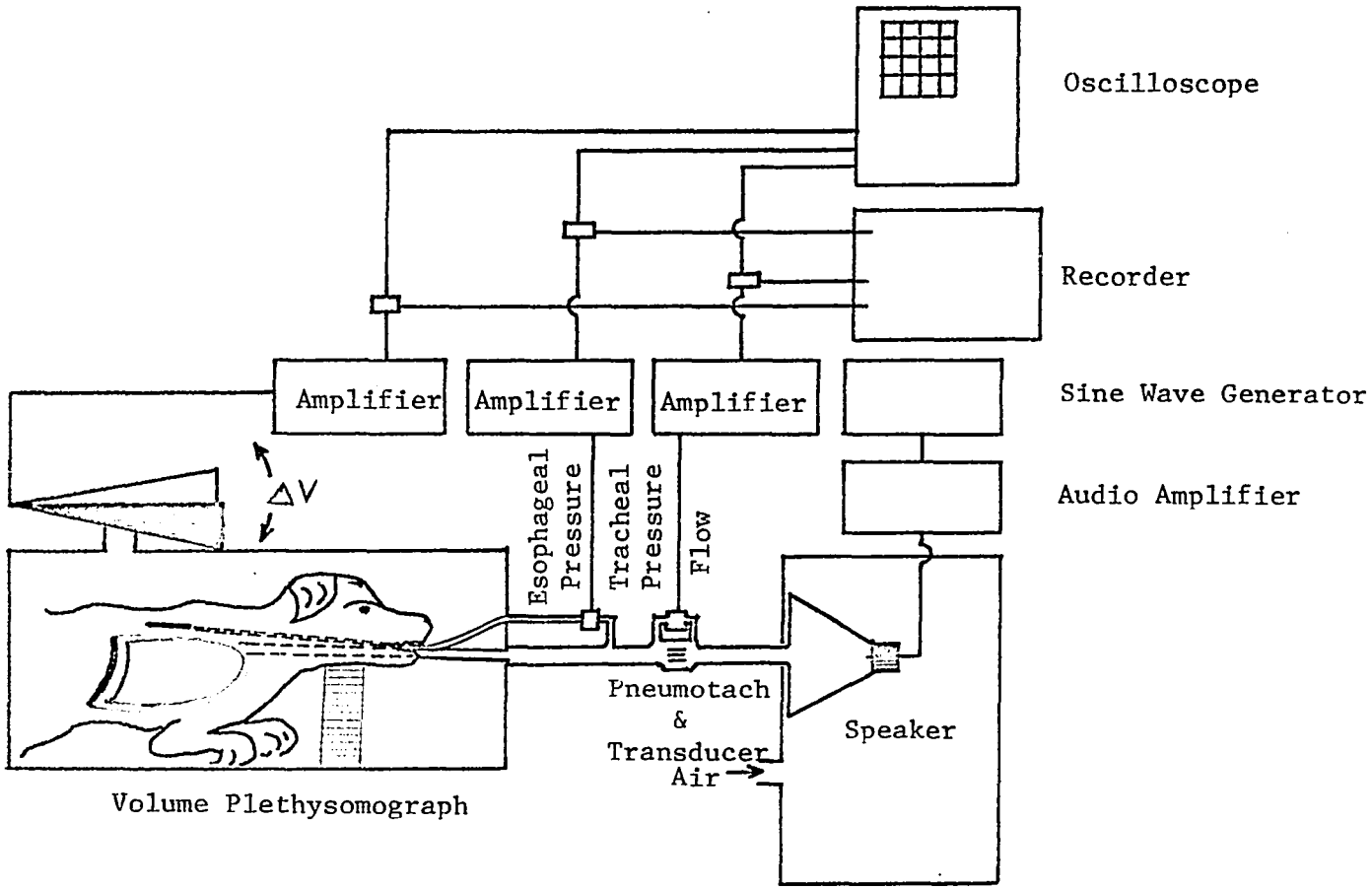


Fig. 1. Block Diagram of System for Measurement of Lung Volumes and Mechanics.

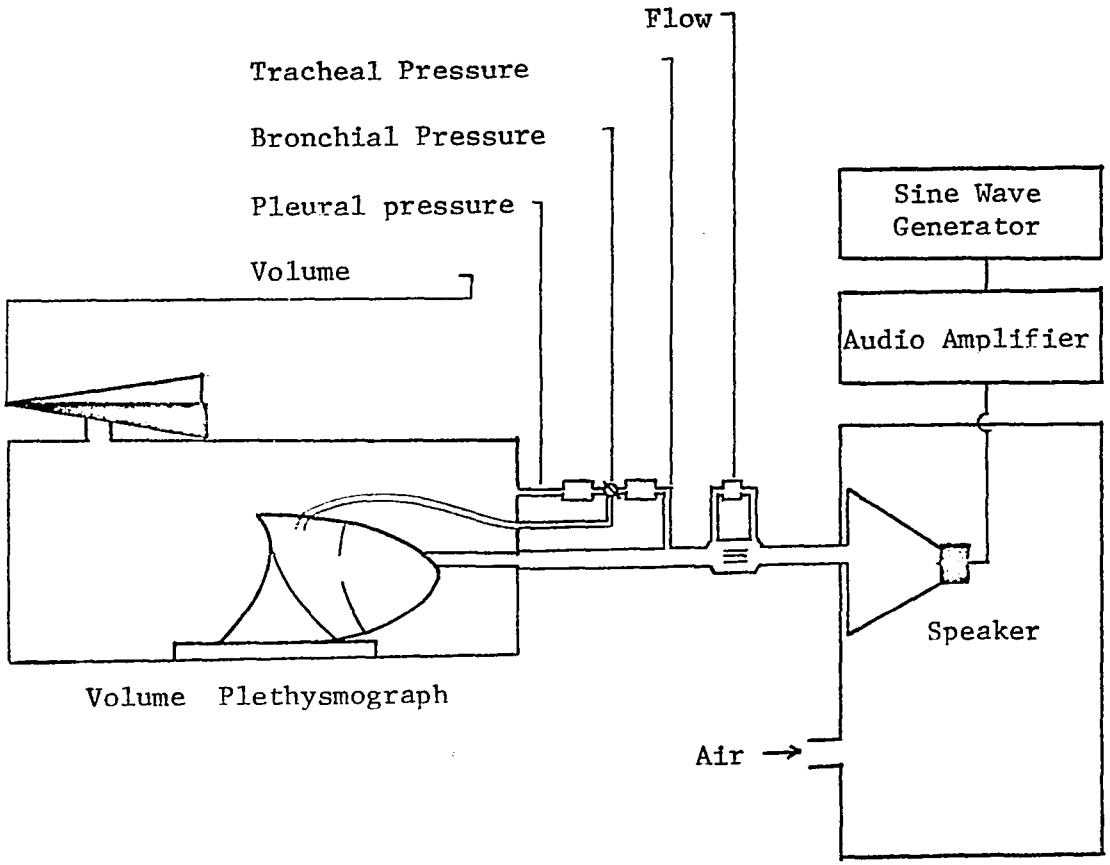
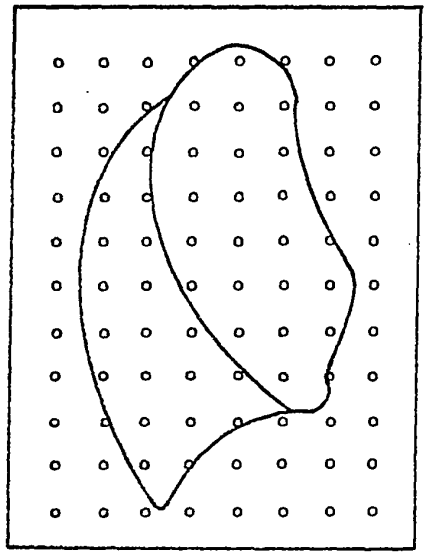
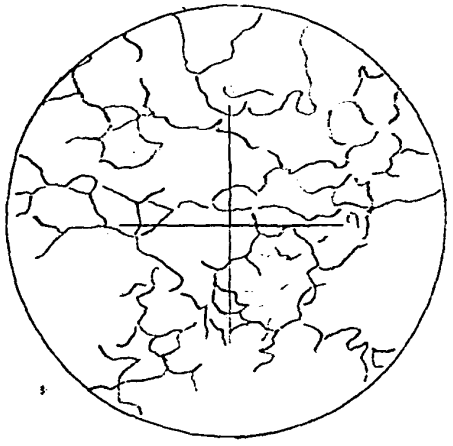


Fig. 2. Circuit Diagram for Measuring Airway Resistance, (Retrograde Catheter Technique).



Grid
(A)



(B)

Fig. 3. (A) Diagram of Stratified Random Point Count.
(B) A Lung Field with Crossed Hair Lines Present in the Eyepiece for Use in the Mean Linear Intercept Method.

RESULTS

Three dogs died after papain injection without any comparative measurement and one dog was found to have pneumonia without emphysema produced. All were excluded from the series.

The results were summarized and presented individually in tables. Control and experimental results were compared for each dog. The group results were the average of the individual values. For the experimental measurements, only the final results were averaged. The difference between both groups was statistically analysed using the "t" test, and if the P value was less than 0.05, the differences were considered significant.

Lung Volume

The individual results are shown in table II and the group results are given in table VI. The VC, FRC, RV and TLC were all increased (except the VC of the dog 10). The VC was increased from 118 to 617 ml and the difference between means was 12.0%. In human emphysema, the vital capacity usually decreased. However, we could not expect to see a decreased vital capacity in these experiments, since we have arbitrarily defined total lung capacity as the volume reached at a transpulmonary pressure of 30 cm of water. The maximum transpulmonary pressure in the emphysematous

TABLE II

Subdivisions of Lung Volume

Dog No.	Period (Days)*	VC (ml.BTPS) C	VC (ml.BTPS) E	VC (ml.BTPS) %	FRC (ml.BTPS) C	FRC (ml.BTPS) E	FRC (ml.BTPS) %	RV (ml.BTPS) C	RV (ml.BTPS) E	RV (ml.BTPS) %	TLC (ml.BTPS) C	TLC (ml.BTPS) E	TLC (ml.BTPS) %
9		1622			1251			257			2579		
	7		1740	6.8		1329	6.2		982	2.6		2722	4.6
10		2191			1280			966			3157		
	7		2049	-6.5		1318	3.0		1116	15.6		3165	+0.3
11		1214			849			624			1838		
	7		1319	8.7		1143	34.5		865	38.8		2184	19.1
13		951			918			758			1709		
	7		1125	7.8		1254	36.6		965	27.2		2090	22.3
16		2332			1789			1320			3655		
	7		2572	10.0		1847	3.2		1380	4.7		3952	8.2
17		1662			1458			950			2614		
	14		2213	33.1		1540	5.7		1107	16.5		3320	27.0
	28		2279	38.1		2070	42.3		1430	50.4		3709	41.9
18		2156			1606			1186			3342		
	14		2296	6.5		1670	3.7		1271	7.2		3567	6.7
	28		2459	14.0		1840	14.5		1382	16.5		3841	14.7
19		1773			1076			710			2483		
	14		1801	1.6		1440	34.4		862	21.6		2663	7.2
	28		2009	13.1		1510	40.7		961	35.5		2970	19.6

% = percentage increased from control; VC = vital capacity; FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity; BTPS = body temperature and pressure, saturated with water vapor; C = control; E = experiment; * = period of studies after papain.

patient can reach much less than normal so that the decreased lung elasticity is not manifested by an increased vital capacity.

Functional residual capacity was elevated by 38 to 612 ml. It showed a progressive increase in dogs 17, 18 and 19. The mean FRC of the control measurements was 1.28±0.12 litre; of the experimental measurements it was 1.54±0.12 litre. It was increased by 22.6% of the control value. The dogs, therefore, exhibited overinflation of the lung in the end expiratory phase.

Residual volume was elevated 2.5 to 480 ml above the control values. The mean of the control values was 0.93±0.08 litre, while that of the experimental values was 1.13±0.08 litre. The emphysema group deviated from the mean of the control by 23.9%. This shows that there was still more air trapped in the lung at the end of forced expiration.

Total lung capacity was increased from 8 to 1095 ml above the control values. The mean value for the control measurement was 2.67±0.24 litres, and for the experimental measurement was 3.07±0.26 litres. The average elevation in emphysema was 16.3% that of the controls.

Resting Diffusing Capacity and Fraction $F_{Ico} - F_{Eco}/F_{Ico}$

Resting diffusing capacity, fractional removal of CO and minute ventilation during spontaneous breathing are shown in tables III and VI. The data showed that the minute volume was not stable, but varied from the control to the experiment states. It seems that the changes of D_{Lco}

TABLE III

Diffusing Capacity, CO (Steady State (STPD)) and Fractional CO uptake, Resting

Spontaneous Breathing

Dog No.	Period (Days)*	Diffusing Capacity, CO (ml.CO/min/mm.Hg) C	E	%**	Fractional CO uptake, ml C	E	%	Minute volume (litres) C	E
9		3.5			.250			3.89	
	7		4.8	37.1		.460	84.0		3.88
10		4.05			.502			2.79	
	7		5.42	33.8		.495	-1.4		3.1
11		5.74			.435			4.38	
	7		1.98	-65.5		.354	-18.6		2.27
13		2.95			.484			1.64	
	7		3.31	12.2		.626	29.4		1.01
16		6.91			.567			2.54	
	7		8.94	29.4		.545	-3.9		4.24

Controlled Minute Ventilation

17		6.40			.454			3.77	
	14		5.54	-13.4		.400	-11.9		3.78
	28		3.51	-45.2		.380	-16.3		3.73
18		7.11			.402			3.82	
	14		6.39	-10.1		.387	-3.7		3.80
	28		3.35	-52.9		.357	-11.2		3.86
19		8.47			.515			3.46	
	14		3.67	-56.7		.417	-19.0		3.47
	28		2.59	-69.4		.301	-41.6		3.50
20	28	5.17			.396			4.03	
			2.38	-54.0		.310	-21.7		4.00

* Period of studies after papain

** Percentage increased or decreased from the control

are dependent on the ventilatory volume. It was obvious in dogs 10 and 16 that the diffusing capacity changed with the volume whereas the fractional removal of CO was unchanged. In contrast, when the minute volume was controlled at the same volume for all periods of measurement, D_{Lco} decreased with the fractional removal of CO. The values progressively decreased when the dog received more papain, and the experimental time was prolonged (table III).

The mean D_{Lco} value for the controls in the latter group was 6.79±0.69 cc/min/mmHg and for the experimentals was 2.96±0.28 cc/min/mmHg. The experimental mean value was decreased 55.4% of the control.

Arterial Blood Gases and Acid Base Balance (Table IV(a), IV(b) & VI)

Hypoxemia was observed in both groups. When the dogs were measured during spontaneous breathing, the mean value of the control Po_2 was 82.21±2.11 mmHg and of emphysema was 71.31±6.4 mmHg. The deviation from control was 13.5% decreased. In the controlled ventilation group, the difference between the mean values of Po_2 was 19.1% that of control. It changed from 78.56±4.95 to 64.12±8.93 mmHg.

The arterial O_2 saturation showed a small deviation of the mean value of the experimental measurements from the controls. The means of the control and the experimental values measured during spontaneous breathing were 91.13±0.32% and 87.94±3.54% respectively, and in the controlled ventilation were 91.81±0.7 and 84.55±6.2%

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TABLE IVa

Arterial Blood Gases Studies during Spontaneous Breathing

Dog No.	Period (days)*	pH			Pco_2, mm.Hg.			HCO_3, mEq./L			Po_2, mm.Hg.			HbO_2 % Sat.			MV, litres	
		C	E	%	C	E	%	C	E	%	C	E	%	C	E	%	C	E
9		7.43			44.5			27.3			81.5			91.1			3.89	
	7		7.43	0.0		38.5	-13.5		25.1	-7.9		60.1	-26.3		88.0	-3.4		3.88
10		7.41			41.0			25.3			90.8			92.8			2.79	
	7		7.37	-0.5		45.5	11.0		25.6	1.4		80.5	-11.3		92.0	-0.8		3.1
11		7.39			37.8			22.5			87.5			91.0			4.38	
	7		7.41	0.3		34.25	-9.3		21.3	-5.3		85.5	-2.3		90.3	-0.8		2.27
13		7.39			38.5			22.85			78.5			90.3			1.64	
	14		7.37	-0.3		48.0	24.7		26.85	17.5		81.0	3.2		89.7	-0.7		1.01
16		7.40			38.3			23.3			77.5			91.1			2.54	
	14		7.40	0.0		41.3	7.8		24.6	5.8		72.0	-7.2		90.1	-1.1		4.24

Pco_2 = arterial carbon dioxide tension; Po_2 = arterial O_2 tension; HbO_2 % Sat = percent saturation of hemoglobin with O_2; mm.Hg. = milimeter of murcury; C = control studies; E = studies after injecting of papain; % = percentage increased or decreased from the control.

* Period of studies after papain. MV = minute volume.

TABLE IVb

Arterial Blood Gases Studies during Controlled Minute Ventilation

Dog No.	Period (days)*	pH			Pco_2, mm.Hg.			HCO_3, mEq./L			Po_2, mm.Hg.			HbO_2 % Sat.			MV, litres	
		C	E	%	C	E	%	C	E	%	C	E	%	C	E	%	C	E
		7.37			32.8			18.7			76.5			91.3			3.77	
17	14		7.39	0.2		35.0	6.9		20.5	10.0		77.0	0.7		90.3	-1.1		3.78
	28		7.37	-0.1		37.0	13.0		21.0	12.6		69.4	-9.3		89.6	-1.8		3.73
		7.43			36.0			23.0			93.0			93.8			3.82	
18	14		7.33	-1.4		45.0	25.0		22.8	-1.1		77.0	-17.2		90.2	-3.8		3.80
	28		7.39	-0.5		34.3	-4.9		20.3	-12.0		80.5	-13.4		91.0	-2.9		3.86
		7.42			35.0			22.1			74.0			91.8			3.46	
19	14		7.42	0.0		30.3	-13.4		19.3	-12.9		83.5	12.8		92.0	0.27		3.47
	28		7.44	0.3		32.6	-7.0		21.5	-2.7		67.9	-8.2		91.6	-0.16		3.50
		7.45			38.3			25.8			70.8			90.5			4.03	
20	28		7.41	0.47		25.6	-33.1		15.5	39.9		38.7	-45.3		66.0	-27.1		4.00

Note: Symbols used are the same as in Table IVa

respectively. The difference between the mean in the first group was 3.5% and in the latter group was 8.0% below the control value.

The arterial Pco_2 varied among the individual dogs. It showed a tendency to increase in the first group while it tended to decrease in the second group. The mean values of the spontaneous breathing group were 39.9±0.94 mmHg and 41.1±3.02 mmHg and in the controlled ventilation group were 35.56±1.13 and 32.35±2.43 mmHg for the control and the experimental studies respectively.

The pH was unchanged in both groups. Plasma bicarbonate was variable. The means of the first group were 24.0±1.71 mEq/L and 25.3±2.2 mEq/L; of the second group 22.39±1.47 and 19.56±1.38 mEq/L for the control and the experimental periods respectively.

Group results showed that there were significant increases in the FRC, RV and TLC at a P level of 0.01.

In the arterial blood gases, Pco_2, Po_2 and O_2 saturation and blood pH and plasma bicarbonate there were no significant changes ($P > 0.05$). Duffusing capacity was significantly decreased in emphysema ($P < 0.01$).

The Mechanics Study

Static compliance. The quasi-static compliance of the dog lungs are shown in table V which includes values obtained from the control periods and the experimental studies. The average results of both groups and statistic calculations are presented (table VI).

TABLE V

Static Lung Compliance and Maximal Negative Intra-Pleural Pressures

Dog No.	Period (Days)*	Compliance (litre/cm.H_2O) C	E	%	Maximal Negative Intra-esophageal Pressure, cm H_2O C	E
9		0.07			-25.5	
	7		0.09	23.3		-16.3
10		0.08			-26.0	
	7		0.10	20.3		-16.3
11		0.05			-22.5	
	7		0.06	18.5		-4.5
13		0.04			-25.0	
	14		0.05	22.5		-9.5
15		0.02			-27.5	
	14		0.05	117.4		-7.5
16		0.09			-30.0	
	14		0.12	44.7		-14.5
		0.05			-27.0	
17	14		0.07	47.8		-9.5
	28		0.10	123.9		-2.5
		0.08			-22.5	
18	14		0.10	28.2		-14.0
	28		0.12	52.6		-9.8
		0.07			-30.0	
	14		0.16	116.4		-13.8
19	28		0.18	146.6		-6.5
		0.11			-	
20	28		0.18	63.64		-

* Period of studies after papain

C = Control

E = Experiment

% = Increased from the control

TABLE VI

Summary of Function Studies

Function test		Mean ± SE Control	Mean ± SE Experiment	P
FRC (litre)		1.28±0.12	1.54±0.12	0.01
RV (litre)		0.93±0.09	1.13±0.08	0.01
TLC (litre)		2.67±0.24	3.07±0.26	0.01
pH	S	7.40±0.01	7.38±0.01	0.3-0.2
	C	7.42±0.02	7.40±0.01	0.4-0.3
Pco_2(mm.Hg)	S	39.90±0.94	44.13±3.01	0.3-0.2
	C	35.56±1.13	32.35±2.43	0.5-0.4
Po_2(mm.Hg)	S	82.21±2.11	71.33±5.2	0.01-0.05
	C	79.68±3.26	70.57±5.26	0.2-0.1
O_2Hb Sat.(%)	S	91.13±0.32	87.94±1.95	0.2-0.1
	C	91.81±0.70	84.55±6.2	0.3
Plasma Bicarbonate (mEq/L)	S	24.00±0.70	25.32±0.90	0.5-0.3
	C	22.39±1.47	19.56±1.38	0.4-0.3
D_{Lco} (ml/min/mmHg)	S	4.63±0.66	4.89±1.05	0.9-0.8
	C	6.79±0.69	2.96±0.28	0.01-0.001
Static Compliance (L/cmH_2O/sec)		0.07±0.01	0.11±0.01	0.01-0.001
Pulmonary Flow Resistance*		4.64±0.33	5.03±0.32	0.7-0.5
R_c (excised lung)*		-	1.57±0.24	—
R_p (excised lung)*		-	3.42±0.62	—
Maximum negative Pressure		-26.2±0.94	-9.7±1.56	0.01-0.001

* At 4 cmH_2O transpulmonary pressure

S = spontaneous breathing

C = control breathing

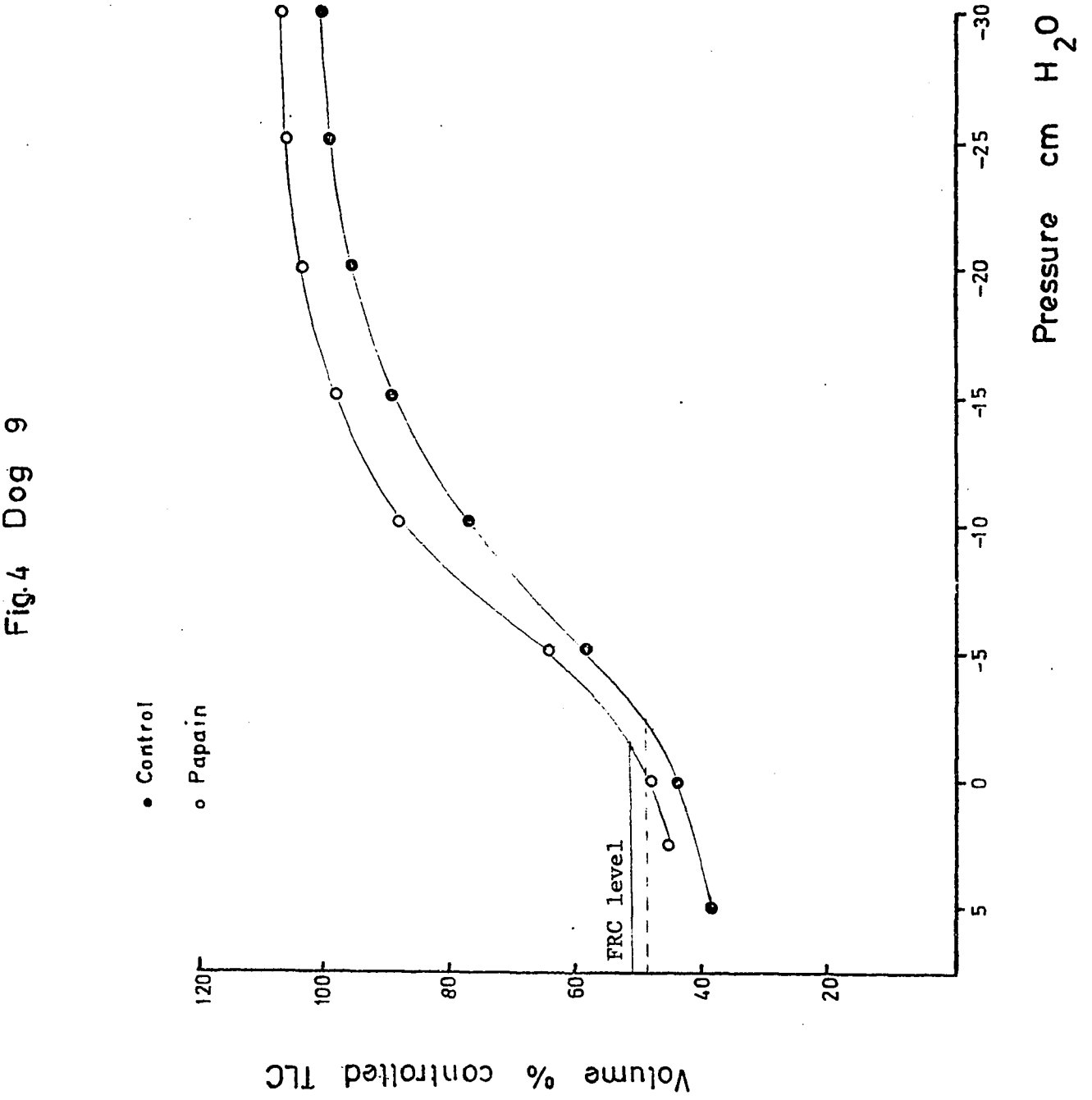

Volume % controlled TLC
120
100
80
60
40
20
FRC level
• Control
o Papain
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H_2O

Fig.4 Dog 9

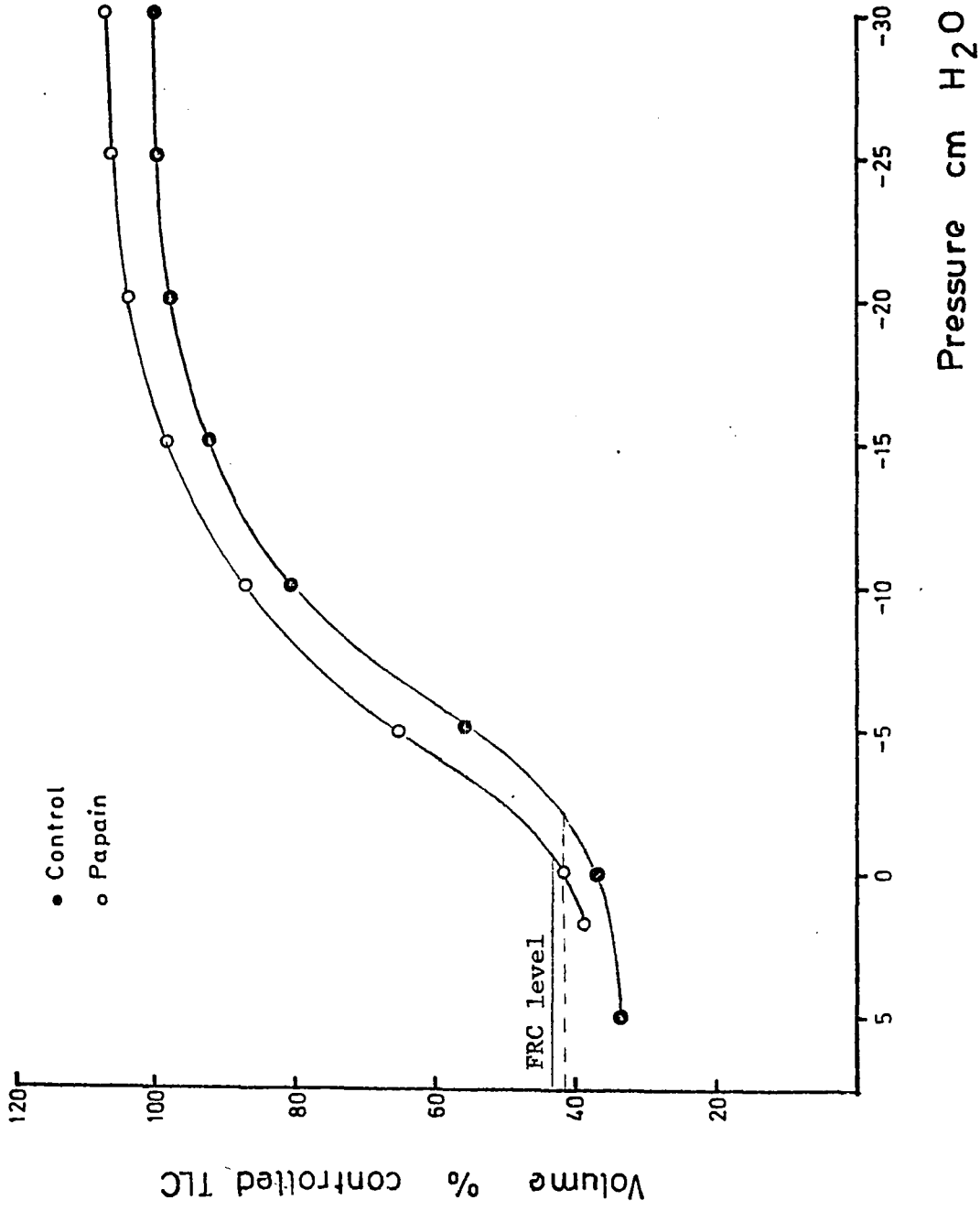

Volume % controlled TLC
120
100
80
60
40
20
FRC level
• Control
o Papain
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H_2O

Fig.5 Dog 10

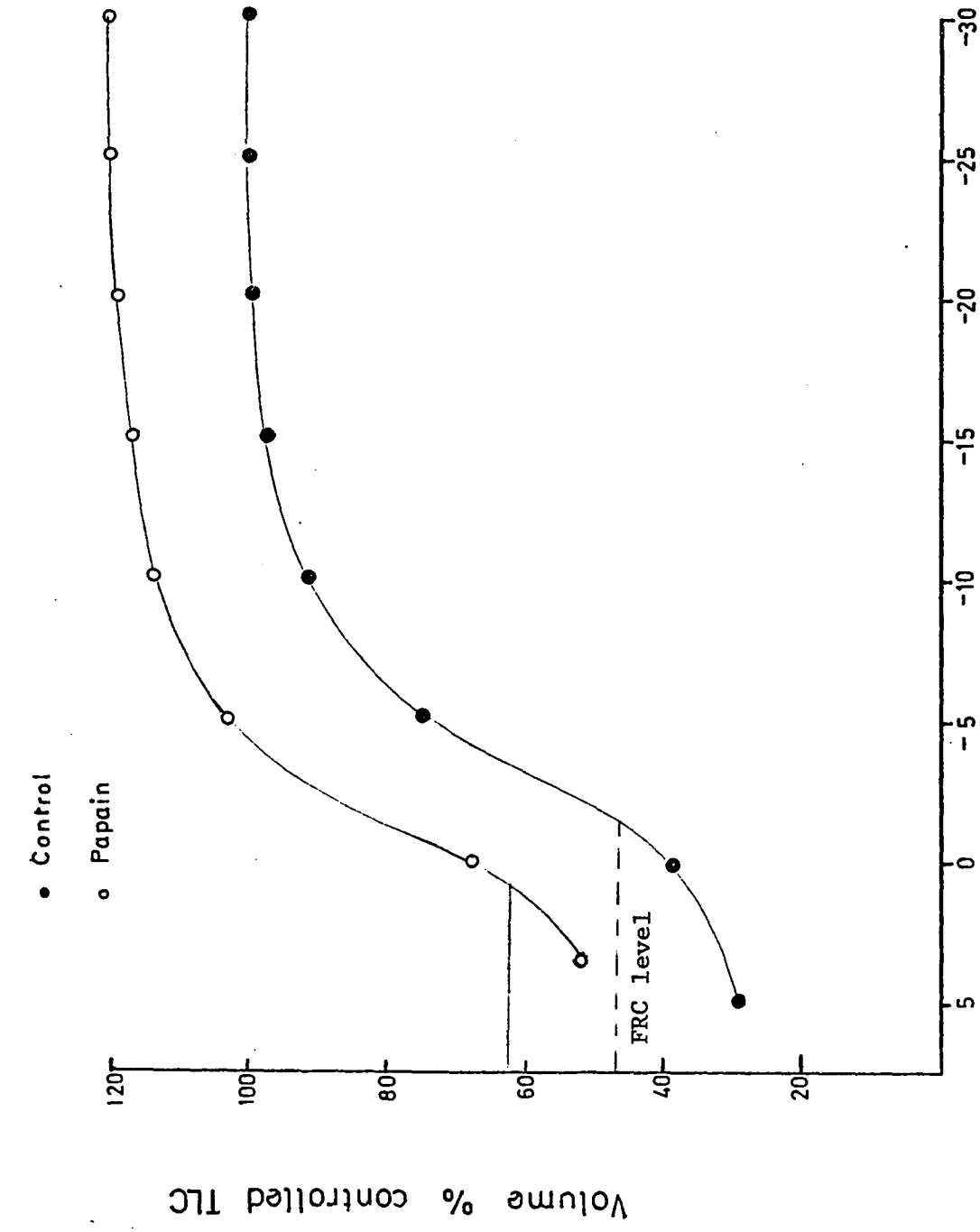
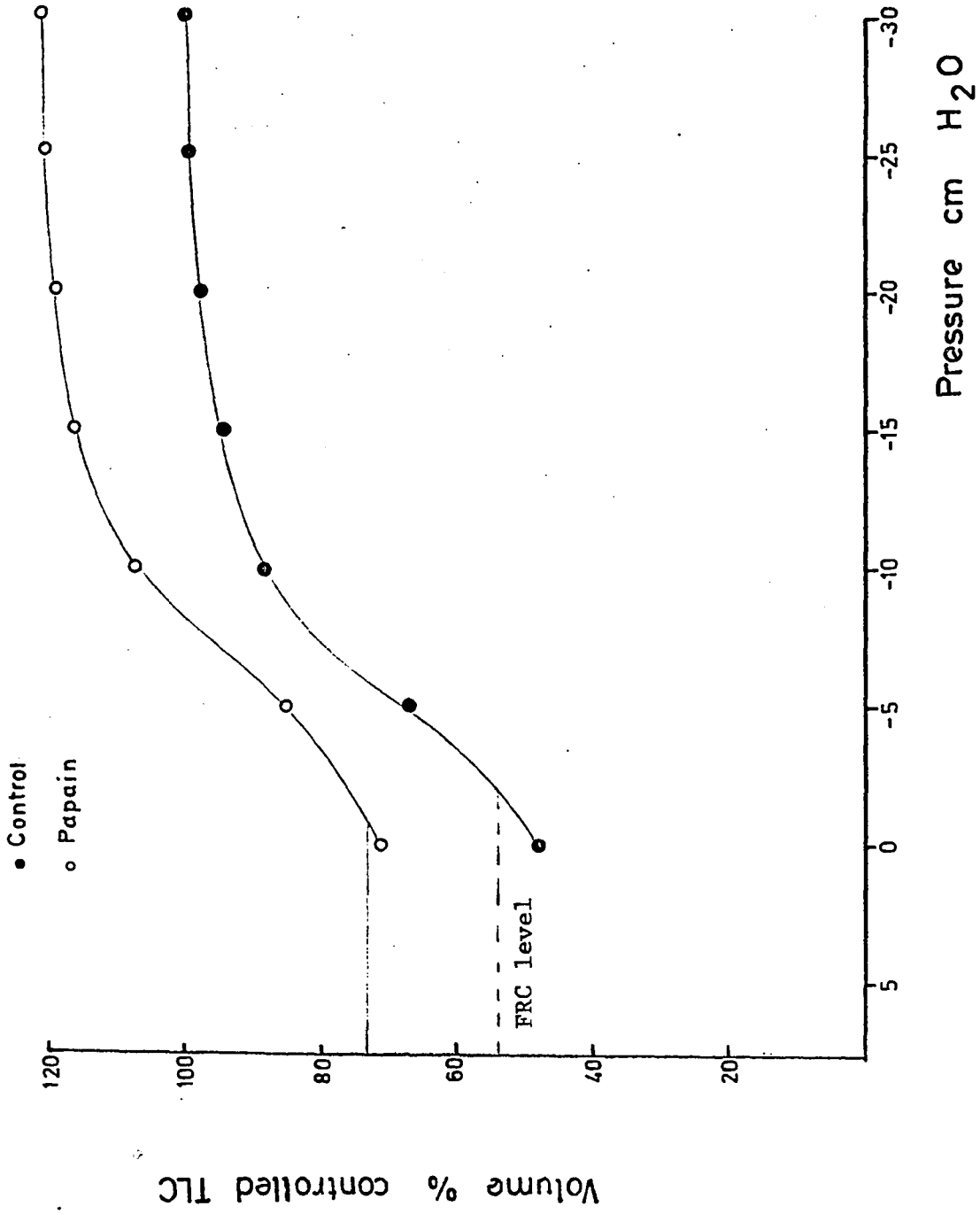

• Control
o Papain
FRC level
Volume % controlled TLC
120
100
80
60
40
20
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H_2O

Fig. 6 Dog 11

Fig.7 Dog 13


• Control
o Papain
FRC level
Volume % controlled TLC
120
100
80
60
40
20
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H_2O

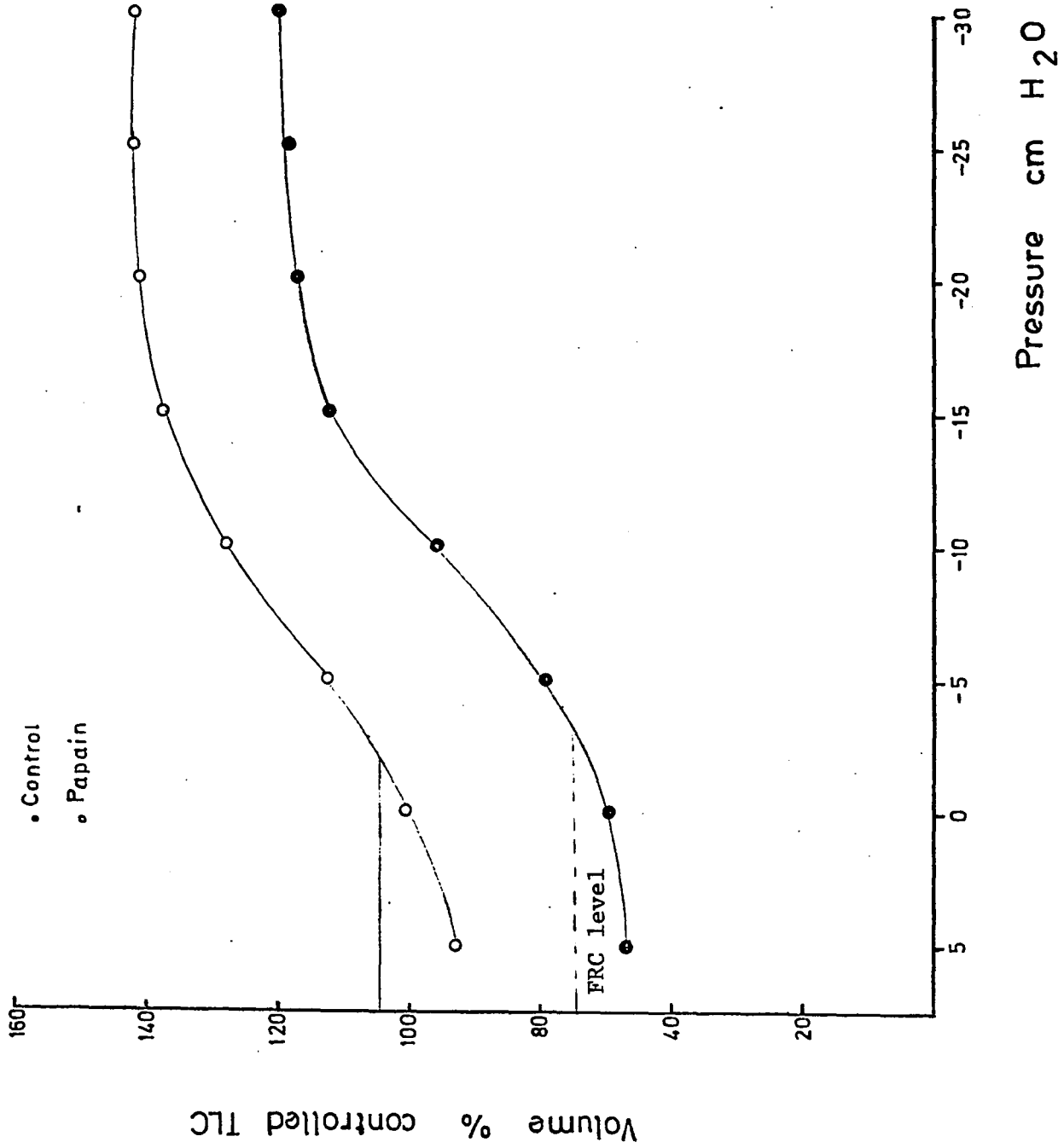

• Control
◦ Papain
FRC level
Volume % controlled TLC
160
140
120
100
80
40
20
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H2O

Fig. 8 Dog 15

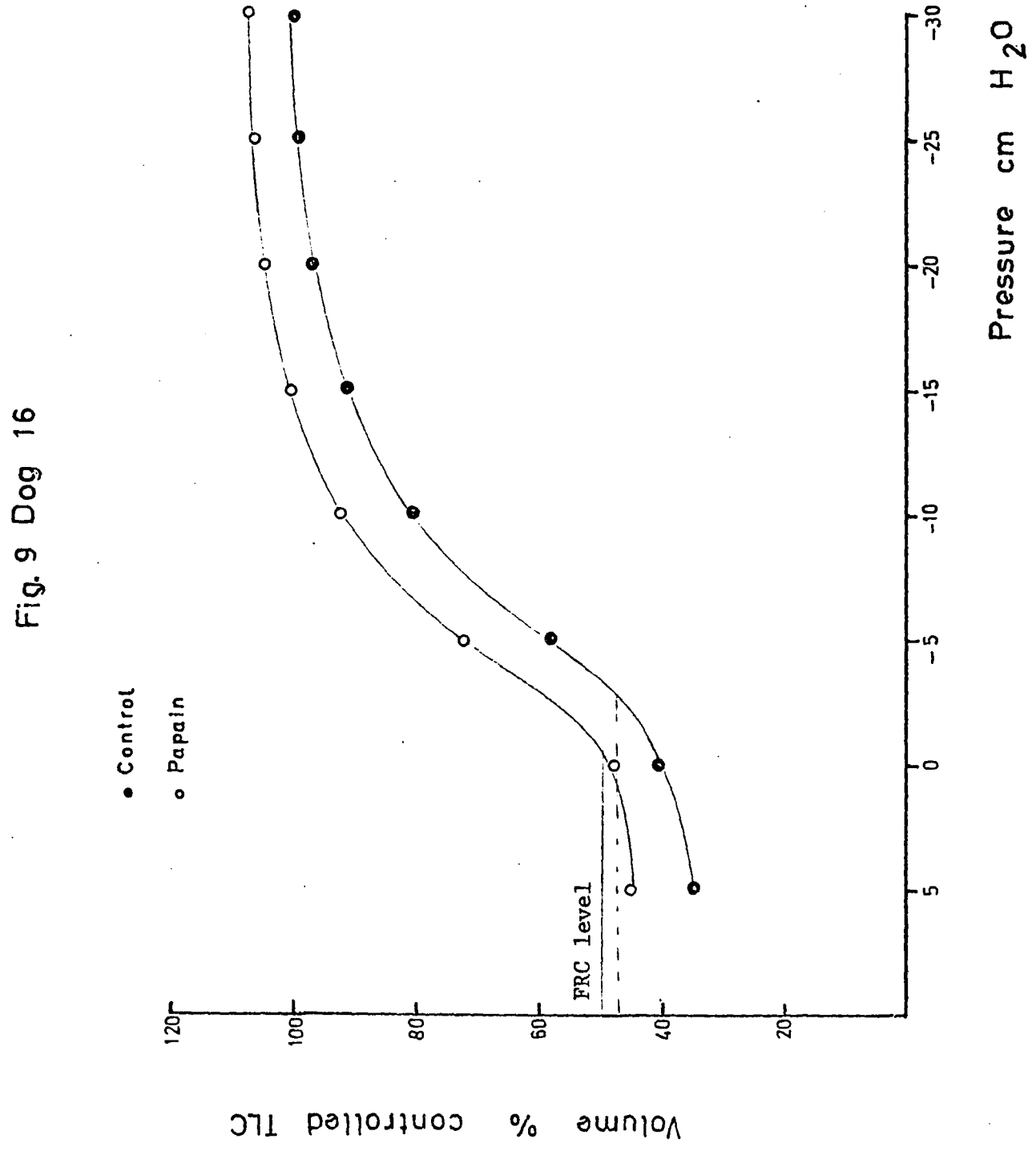

Volume % controlled TLC
120
100
80
60
40
20
FRC level
• Control
o Papain
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H_2O

Fig. 9 Dog 16

Fig.10 Dog 17

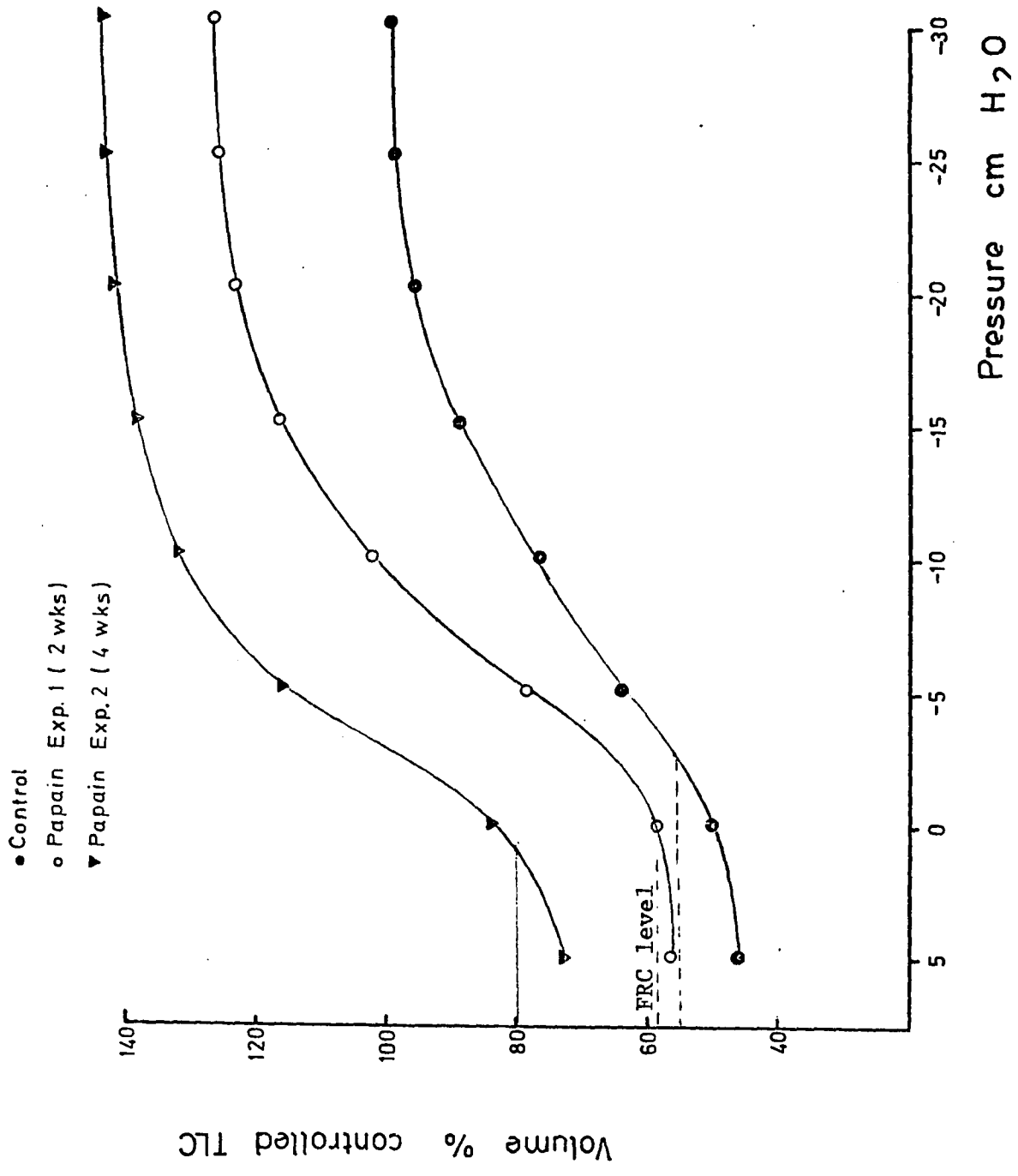
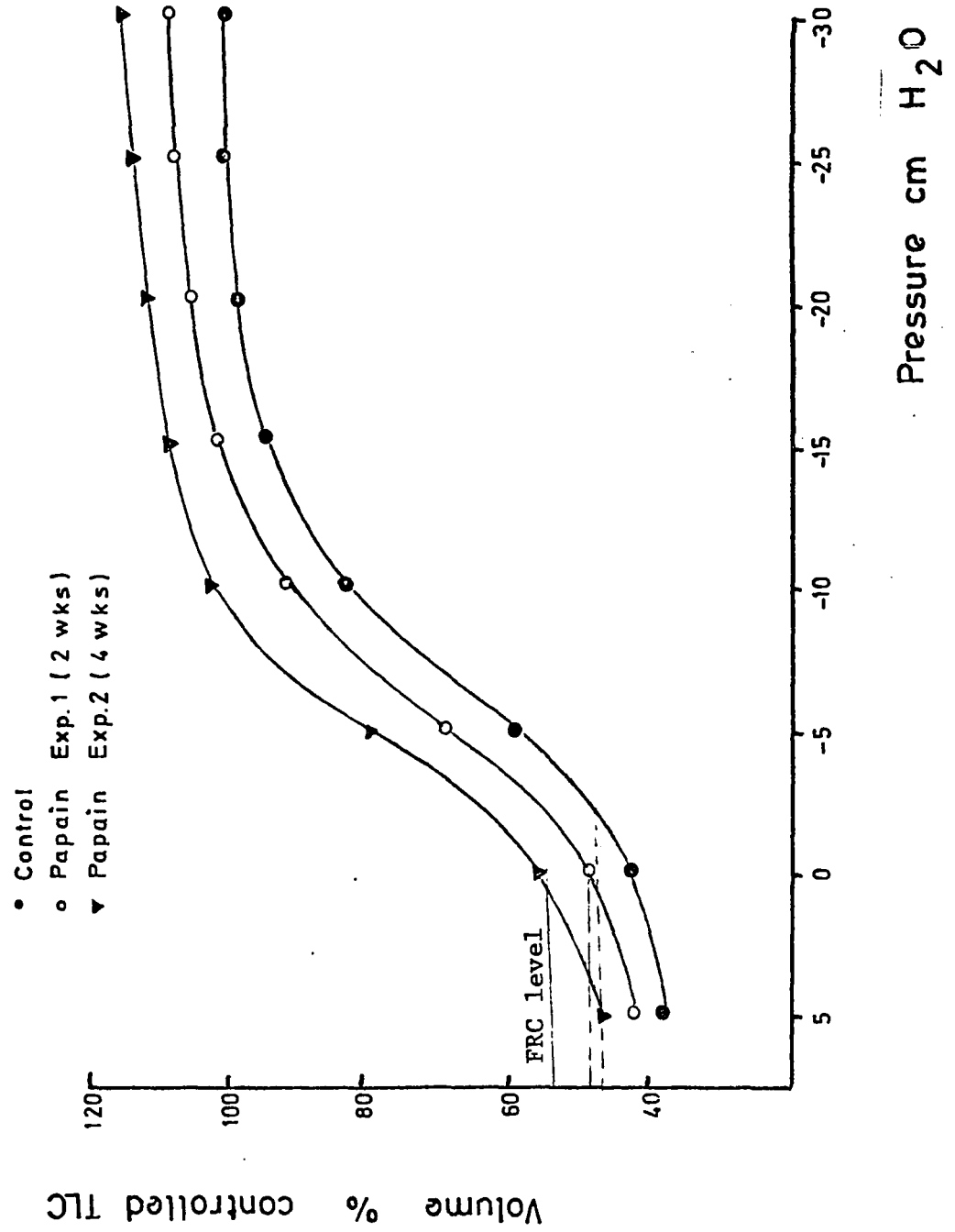

• Control
o Papain Exp. 1 (2 wks)
▼ Papain Exp. 2 (4 wks)
Volume % controlled TLC
140
120
100
80
60
40
FRC level
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H2O

Fig 11 Dog 18


• Control
o Papain Exp.1 (2 wks)
▼ Papain Exp.2 (4 wks)
FRC level
120
100
80
60
40
Volume % controlled TLC
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H_2O

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OMITTED
IN NUMBERING

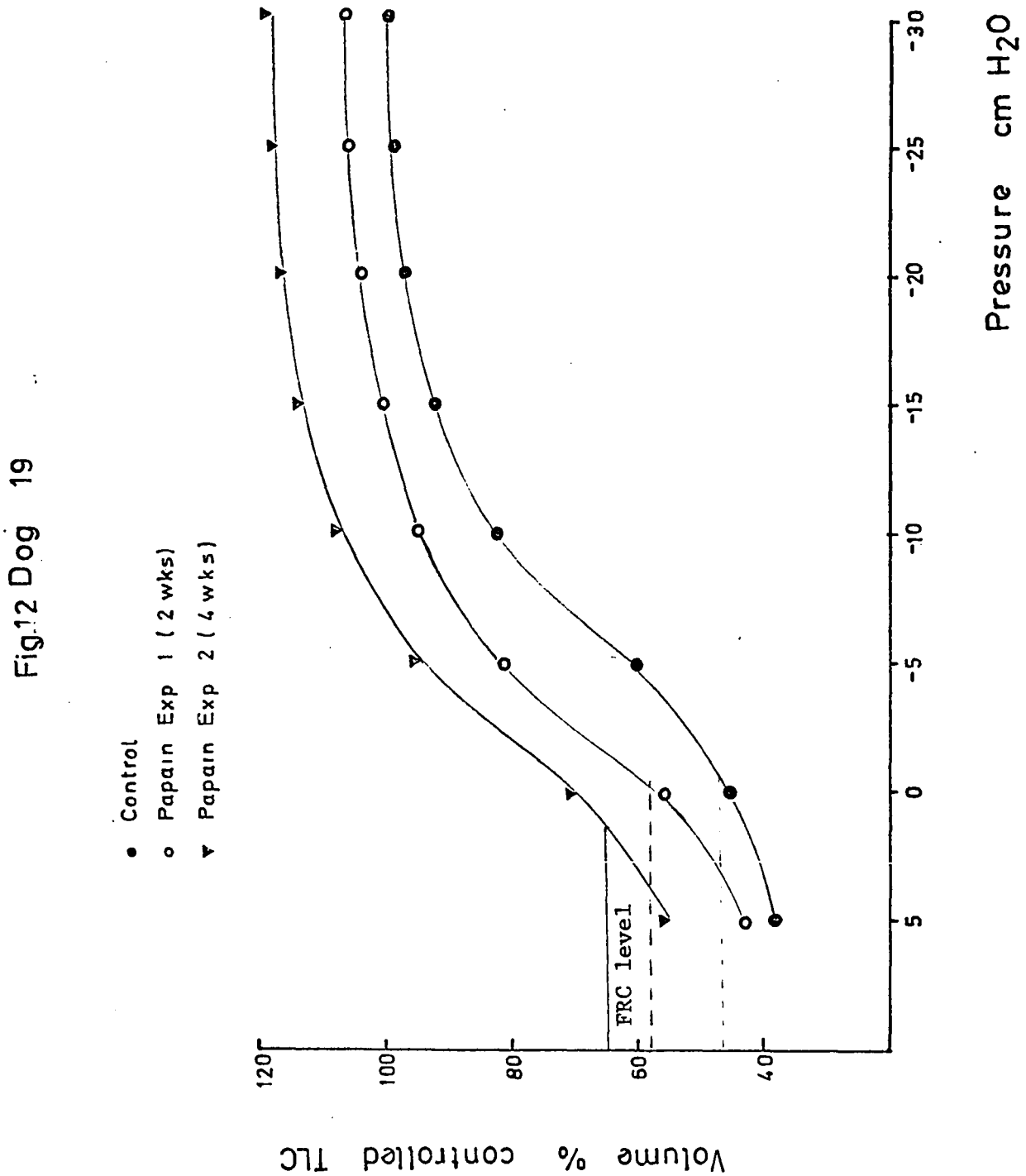


Fig.12 Dog 19
• Control
o Papain Exp 1 (2 wks)
▼ Papain Exp 2 (4 wks)
Volume % controlled TLC
120
100
80
60
40
FRC level
5
0
-5
-10
-15
-20
-25
-30
Pressure cm H2O

Emphysema dogs showed hypercompliance which was increased from 18.5 to 146.6% of the control value. The mean of the control measurements was 0.07±0.02 litre/cm H_2O while that of the experimental studies was 0.11±0.04 litre/cmH_2O. It was elevated by 63.5% of control. The differences between the control and experimental values are statistically significant ($0.01 > P > 0.001$).

The overall volume pressure relationship is illustrated in Figs 4-12. The deflation curve of the control and of the experimental studies were compared individually. As shown, the slope of the pressure volume relationship of the experimental dogs was steeper and shifted upward. The experimental lungs reached a given volume at lower distending pressures than the controls, which was indicated by the loss of the recoil pressure of the lung in emphysema.

The greatest negative pressure is compared at the maximum volume (at distending pressure of 30 cmH_2O) of the control and the results are given in table V. Statistical analyses are shown in table V. The data point out that end inspiratory pressure was less negative in emphysema. The mean value of the control was -26.2±0.94 cmH_2O; of the experimental -9.7±1.56cmH_2O and there was a significant difference between the means.

Resistance

Total pulmonary resistance at various transpulmonary pressures are given in table A1. The resistance and pressures plotted are shown

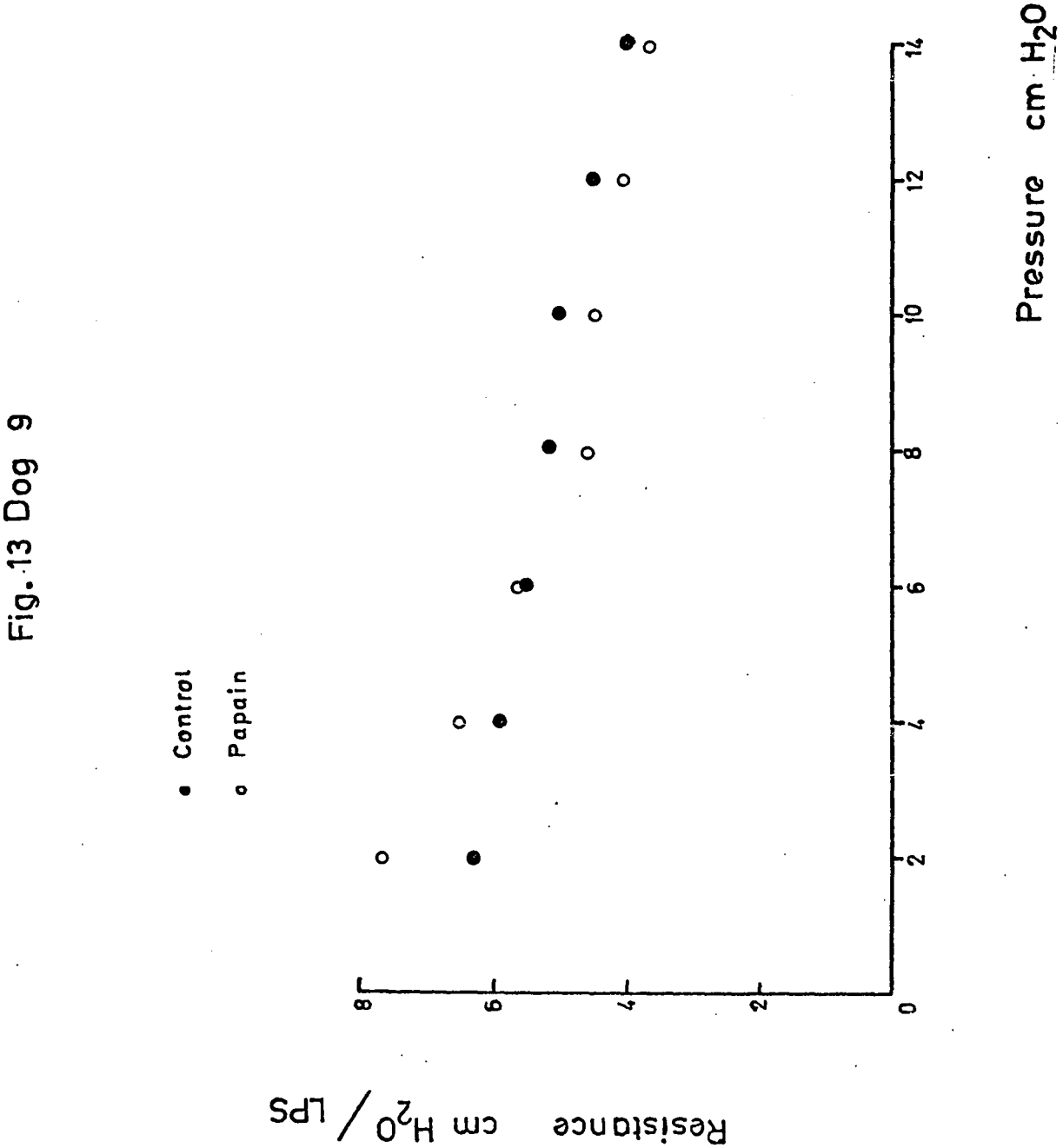

Resistance cm H2O / LPS
8
6
4
2
0
2
4
6
8
10
12
14
Pressure cm H2O
• Control
o Papain

Fig. 13 Dog 9

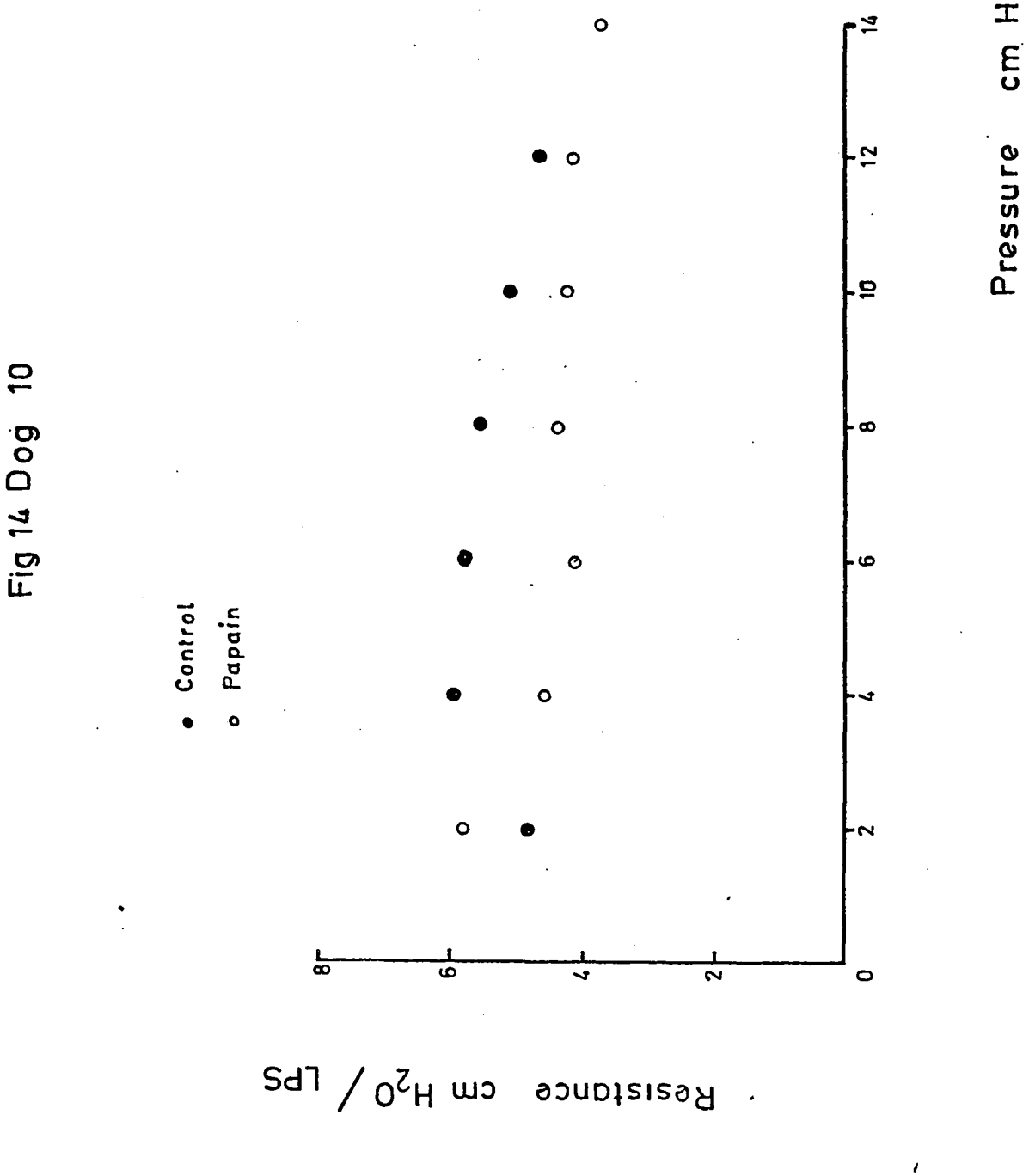

Resistance cm H2O / LPS
Pressure cm H2O
Control
Papain
0
2
4
6
8
10
12
14

Fig 14 Dog 10

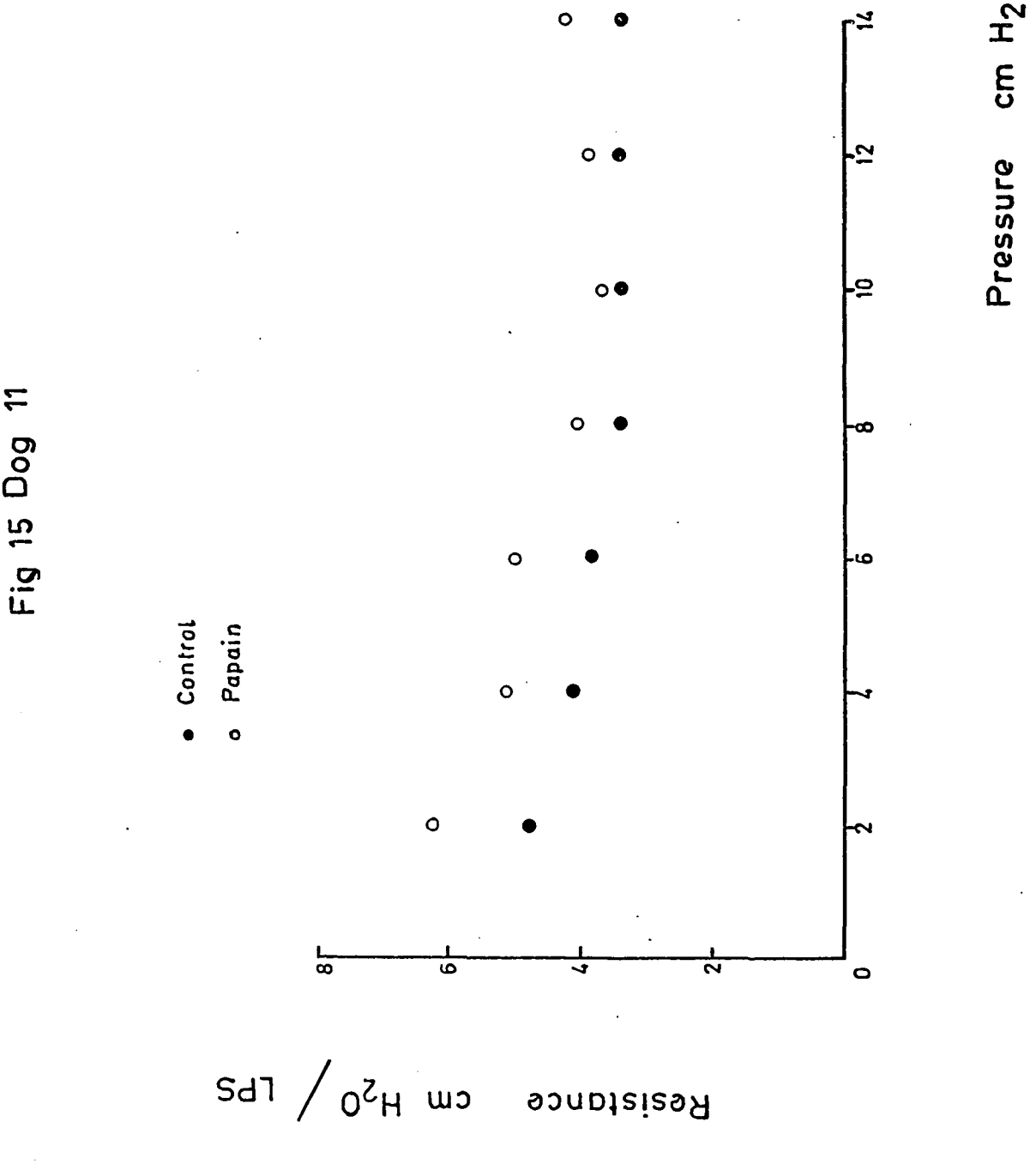
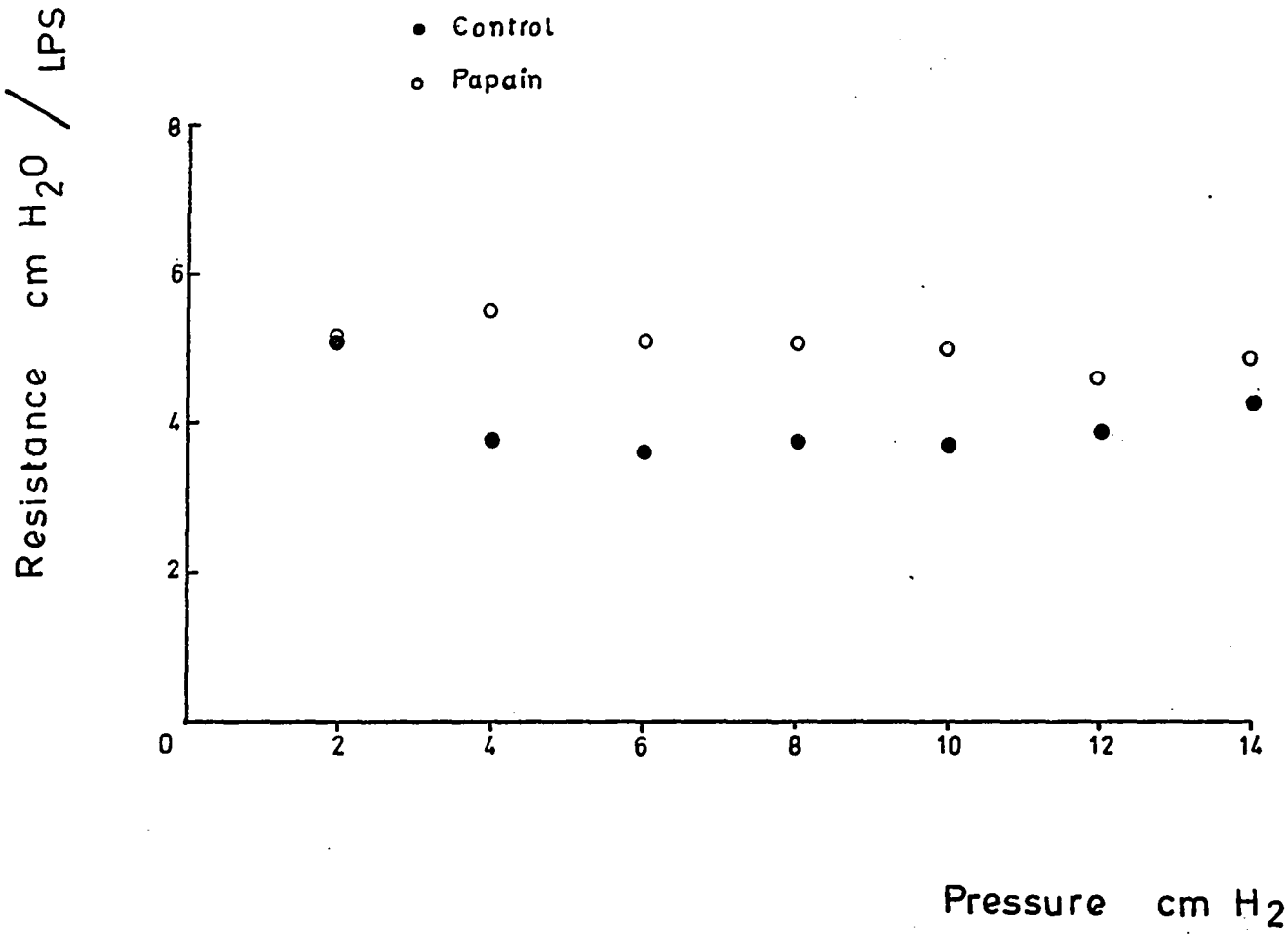

Resistance cm H2O / LPS
Pressure cm H2O
Control
Papain
0
2
4
6
8
10
12
14

Fig 15 Dog 11

Fig 16 Dog 13


Control
Papain
Resistance cm H_2O / LPS
8
6
4
2
0
2
4
6
8
10
12
14
Pressure cm H_2O

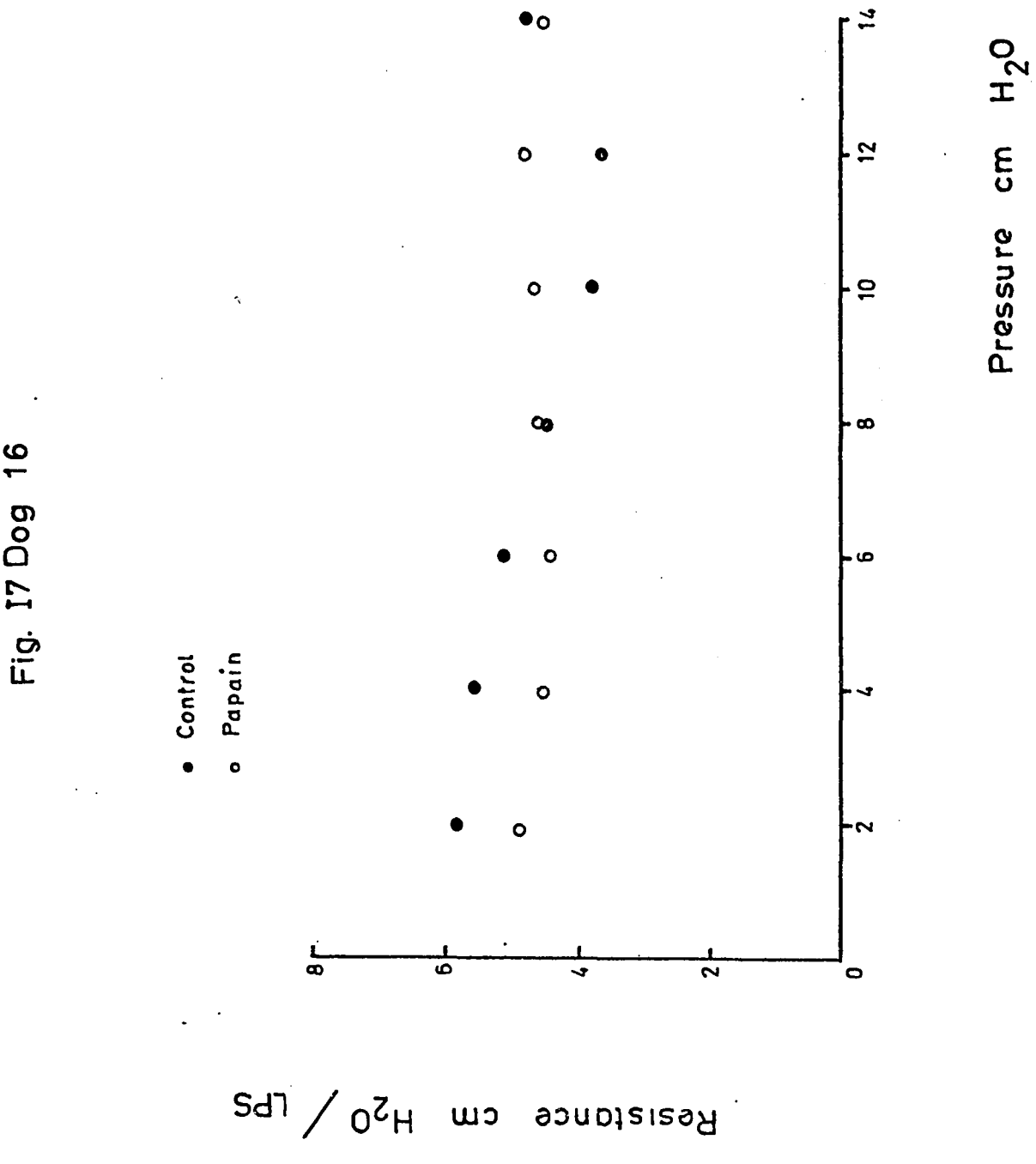

Resistance cm H2O / LPS
8
6
4
2
0
2
4
6
8
10
12
14
Pressure cm H2O
• Control
o Papain

Fig. 17 Dog 16

Fig. 18 Dog 17

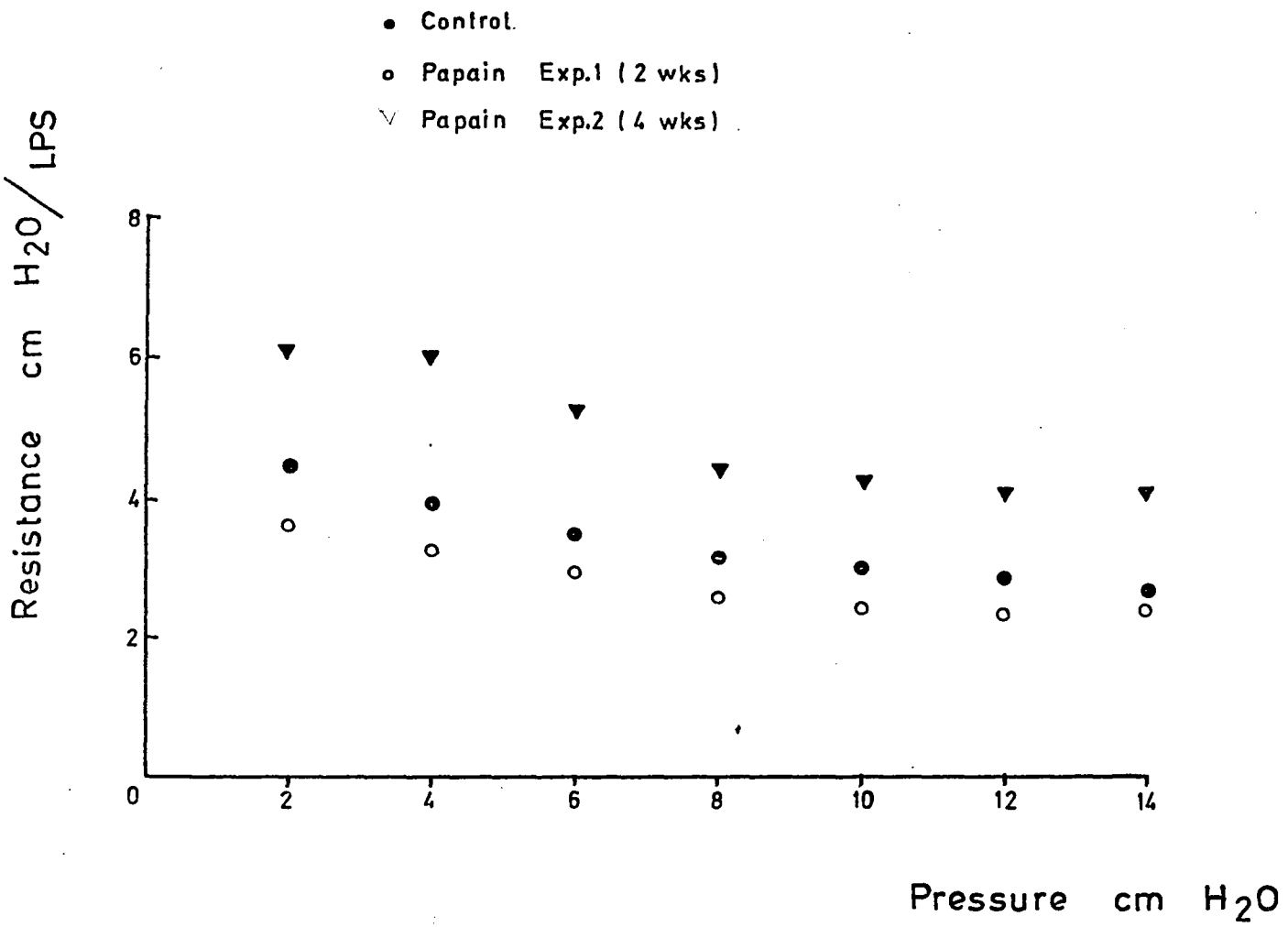

Control
Papain Exp.1 (2 wks)
Papain Exp.2 (4 wks)
Resistance cm H2O / LPS
0
2
4
6
8
2
4
6
8
10
12
14
Pressure cm H2O

Fig. 19 Dog 18

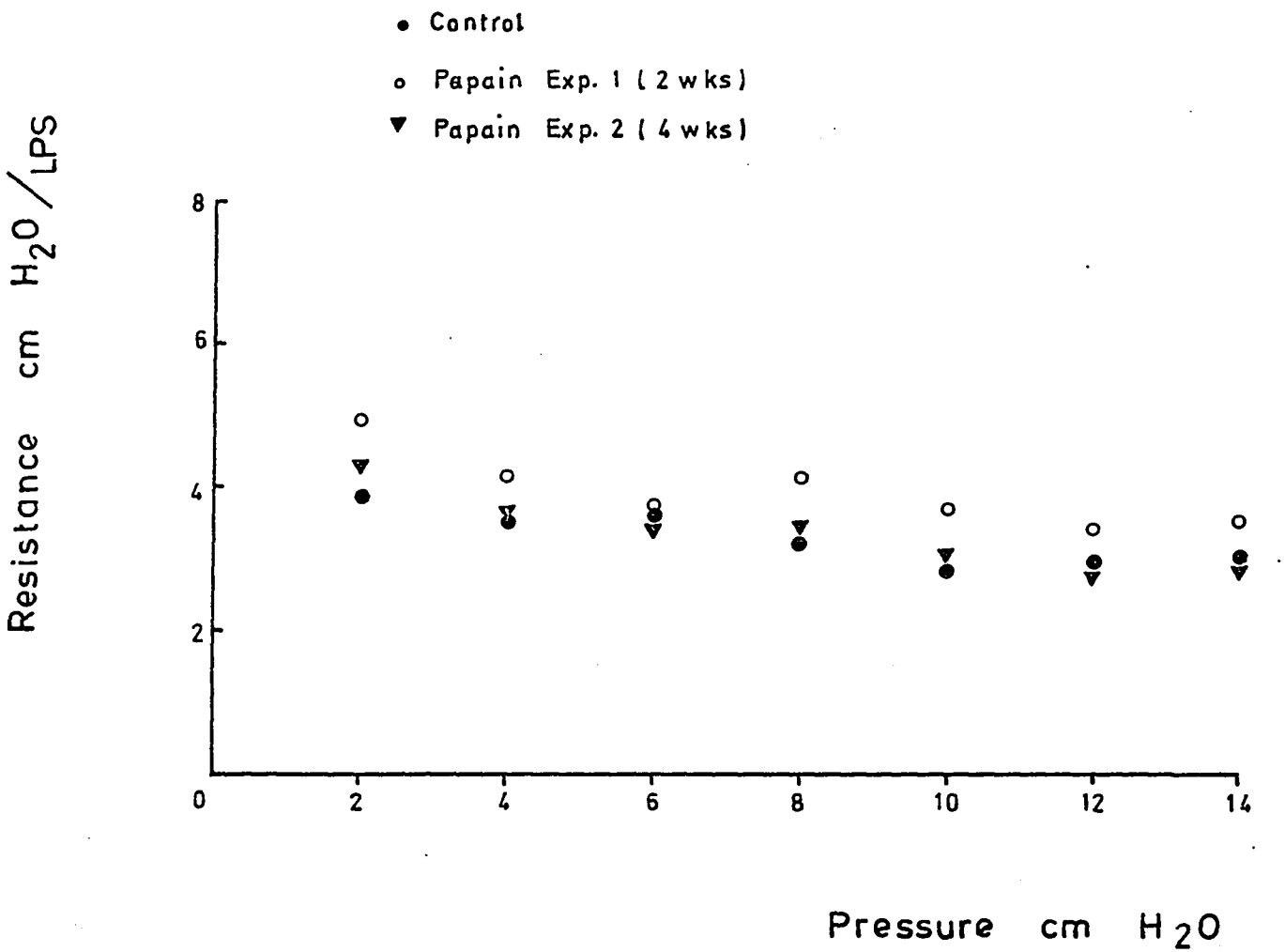
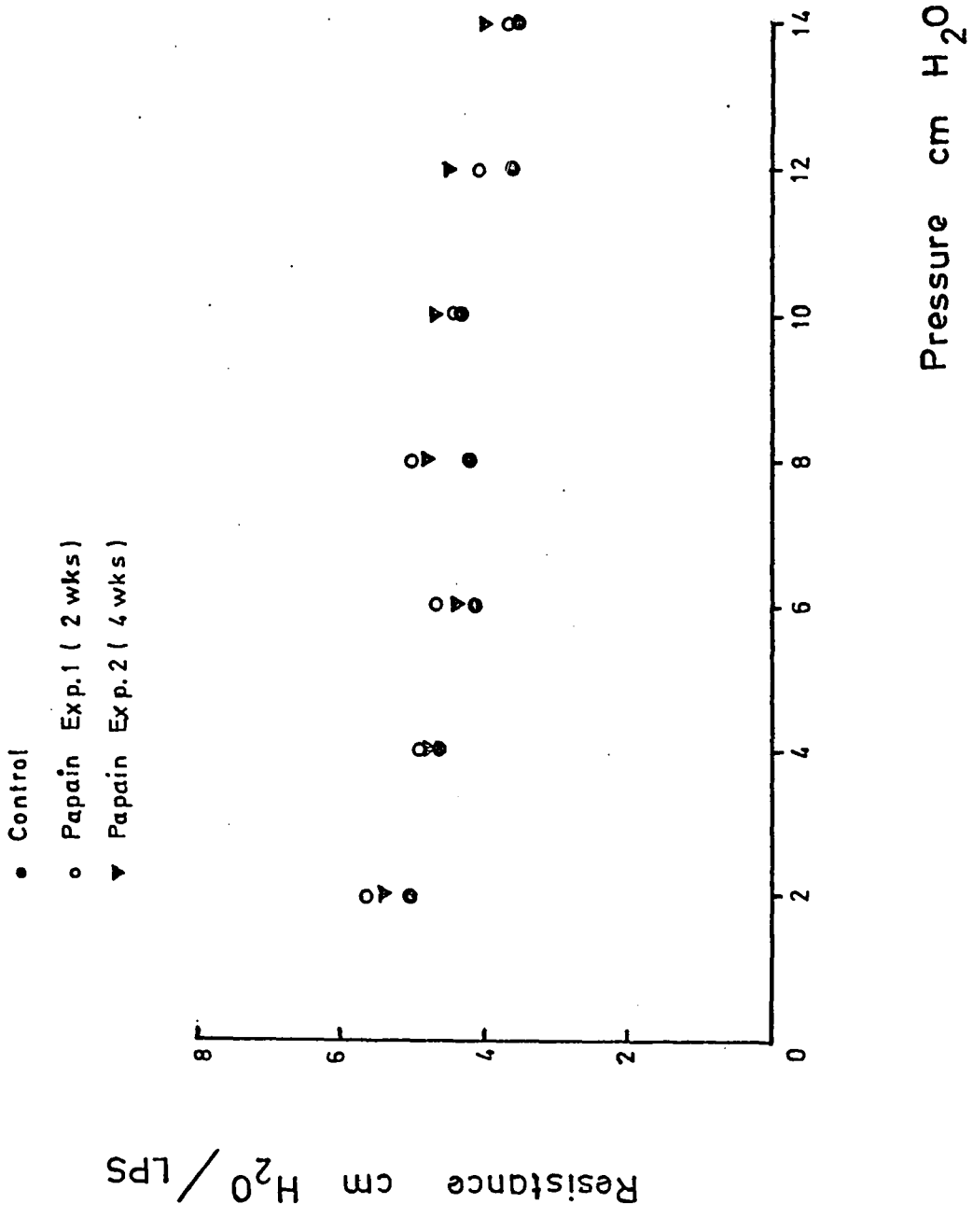

• Control
o Papain Exp. 1 (2 wks)
▼ Papain Exp. 2 (4 wks)
Resistance cm H_2O / LPS
8
6
4
2
0
2
4
6
8
10
12
14
Pressure cm H_2O

Fig. 20 Dog 19


• Control
o Papain Exp.1 (2 wks)
▼ Papain Exp.2 (4 wks)
Resistance cm H_2O / LPS
Pressure cm H_2O
0
2
4
6
8
10
12
14

individually in figs. 13-20. It was increased in dogs 9, 11, 13, 17. A large increase was observed in dog 17, while there was no increase in dogs 10, 16, 18 and 19. The group analysis showed no difference between means of the control and of the experimental data (table A3). This is in contrast to the data obtained from the excised lungs which are given in table A2. The changes of resistance were plotted against related pressure and are illustrated in Figs.21-28.

R_c and R_p were high at lower and higher lung volumes, and decreased to a minimum of transpulmonary pressures at 6 to 8 cm of water. R_p was comprised of 32.5 to 83.7% of R_L at 4cmH_2O distending pressure. Macklem and Mead (75) found that in normal dogs, R_p was too small to detect above 80% VC, but increased at lower lung volumes to 15% of R_L. It was obvious that the present values were definitely increased. This indicated that the increased airway resistance in emphysema of this present study was mostly in the small airways.

Bronchography and Bronchial Diameter Measurement

Bronchography was done on 6 normal excised lungs and in 5 experimental excised lungs (dogs16-20). Bronchial deformity was examined by comparing the bronchial filling of emphysematous lungs with normal lungs. The study revealed that only a few small airways appear occluded with blunt ends and some tapering with slightly dilated small air-ways. These observations were presented in dog 20 and rare in dogs 17, 18 and 19. Dog 16 showed a normal bronchogram. The bronchiectasis was also observed in the right upper lobe of dog 20 (Fig. 29).

Fig 21 Dog 11

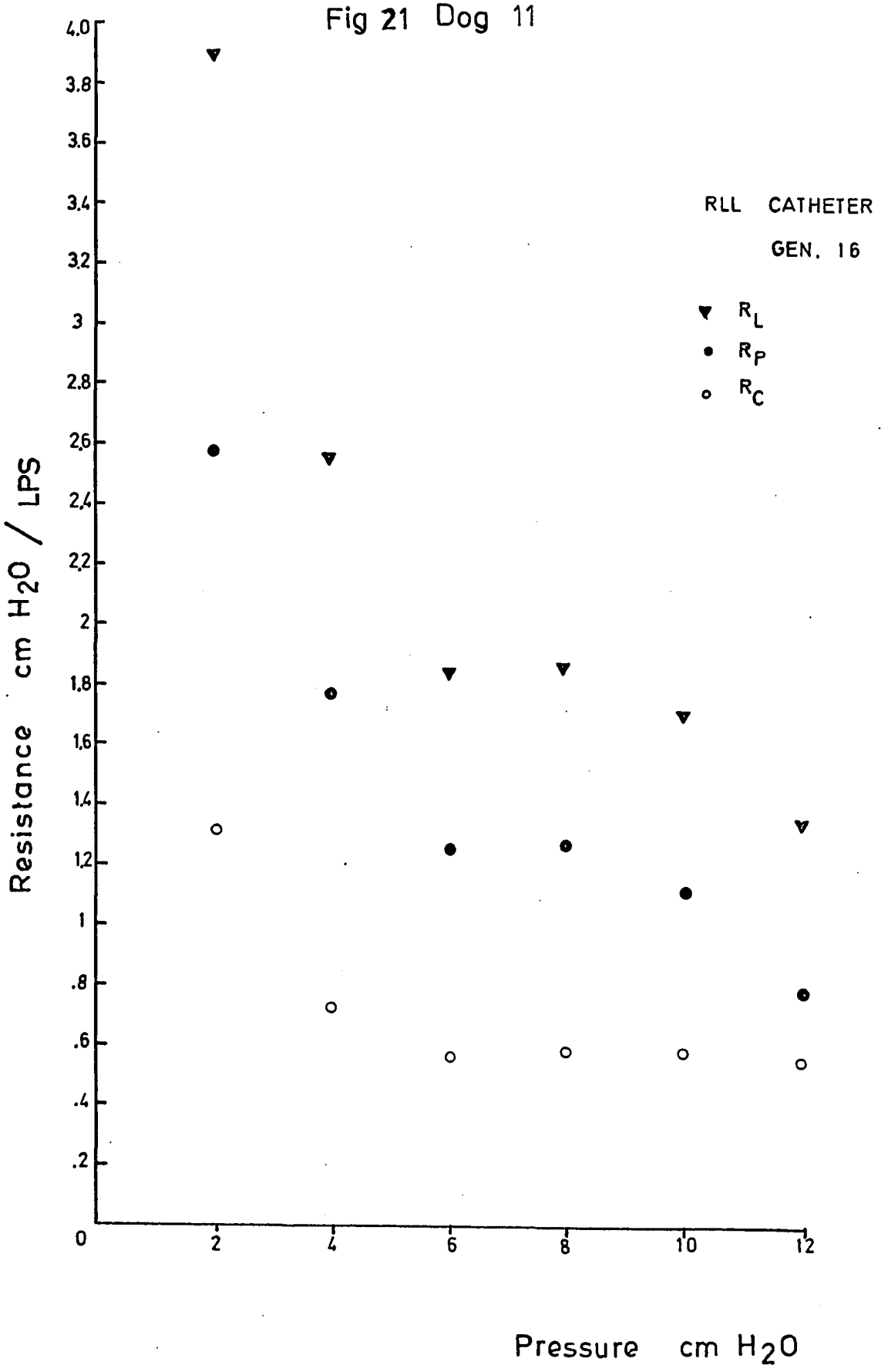

RLL CATHETER
GEN. 16
R_L
R_P
R_C
Resistance cm H_2O / LPS
4.0
3.8
3.6
3.4
3.2
3
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
.8
.6
.4
.2
0
2
4
6
8
10
12
Pressure cm H_2O

Fig. 22 Dog 13

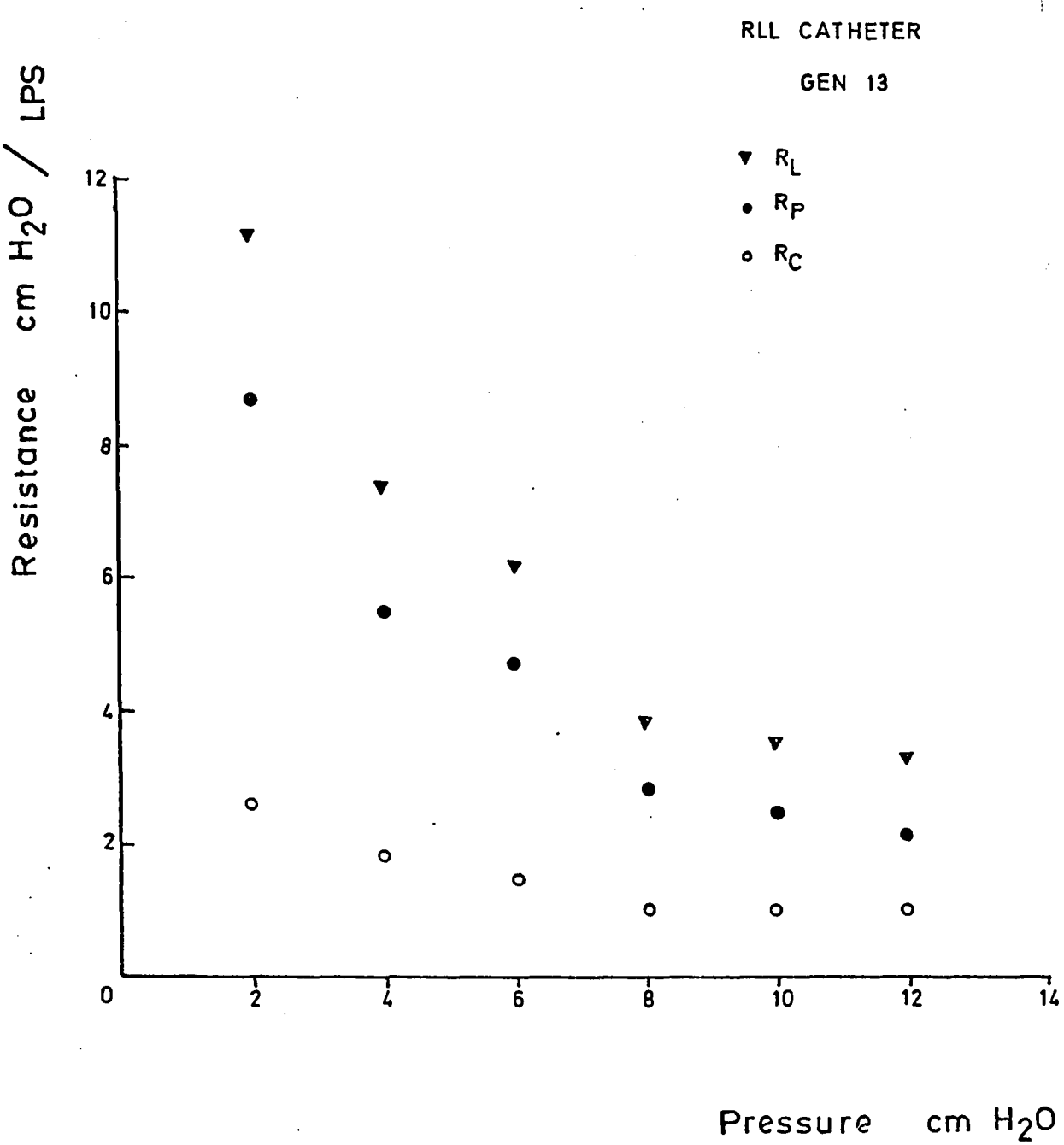

RLL CATHETER
GEN 13
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
10
12
14
Pressure cm H_2O

Fig. 23 Dog 15

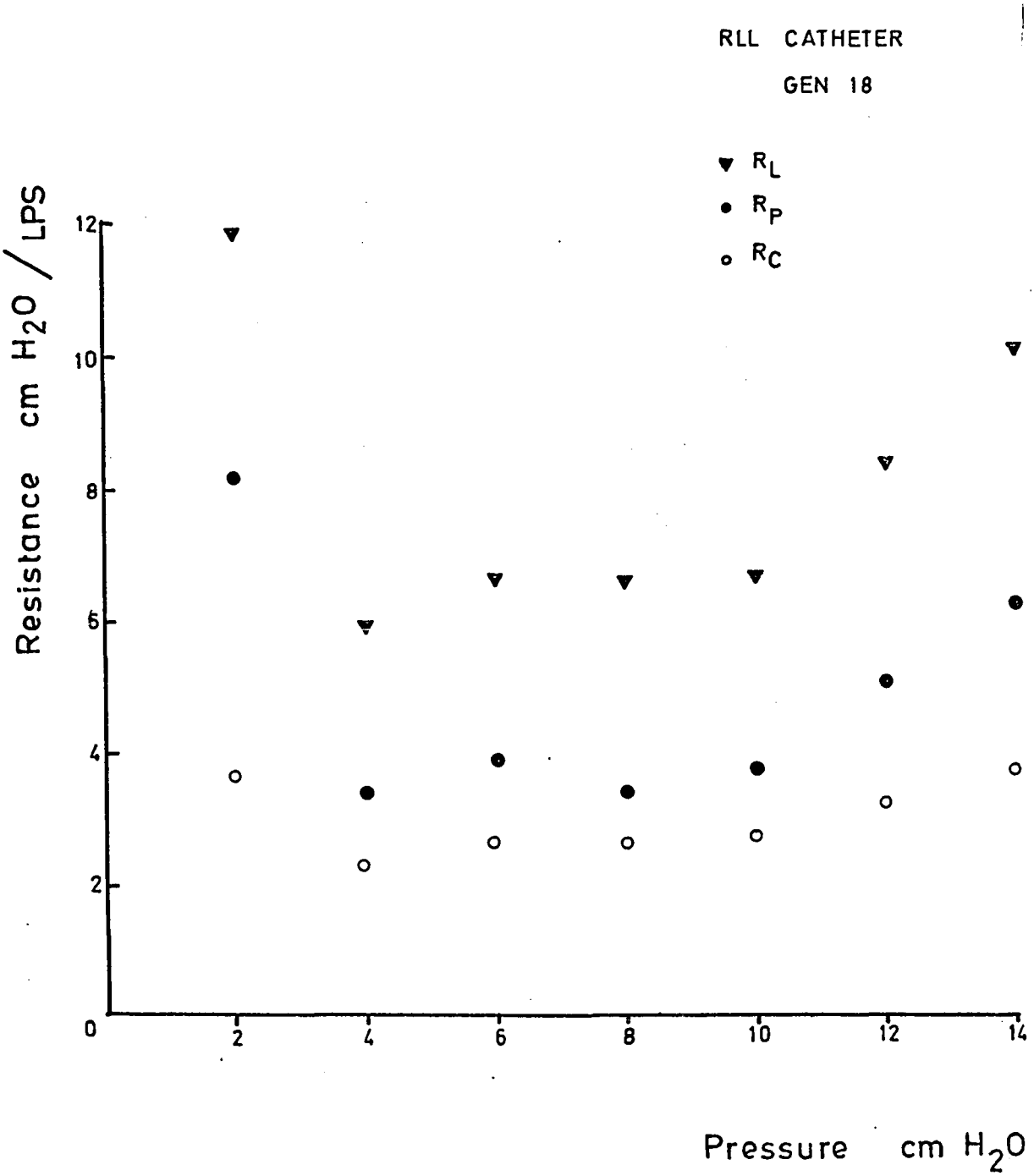

RLL CATHETER
GEN 18
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
10
12
2
4
6
8
10
12
14
Pressure cm H_2O

Fig. 24 Dog 16

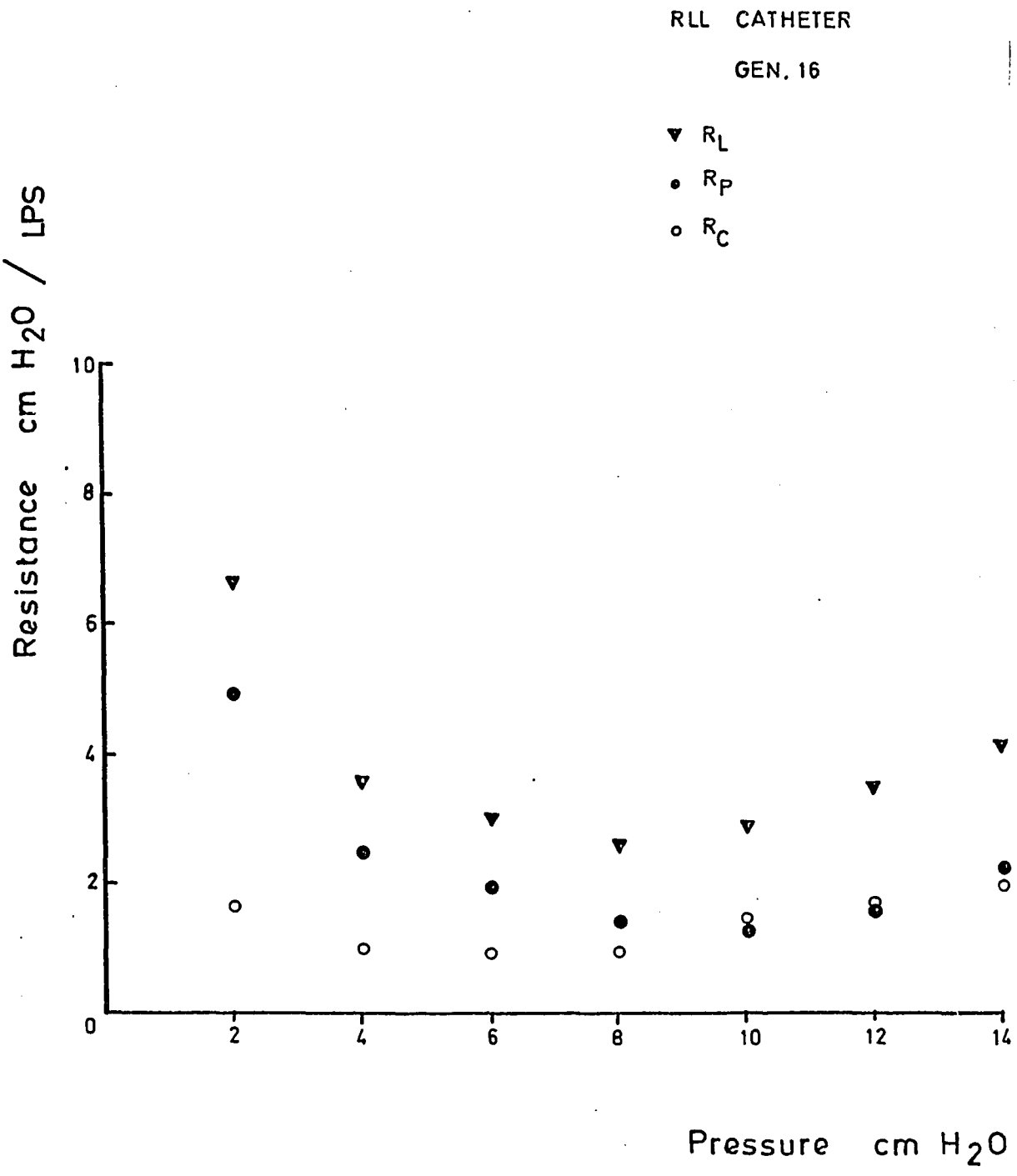

RLL CATHETER
GEN. 16
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
10
2
4
6
8
10
12
14
Pressure cm H_2O

Fig. 25 Dog 17

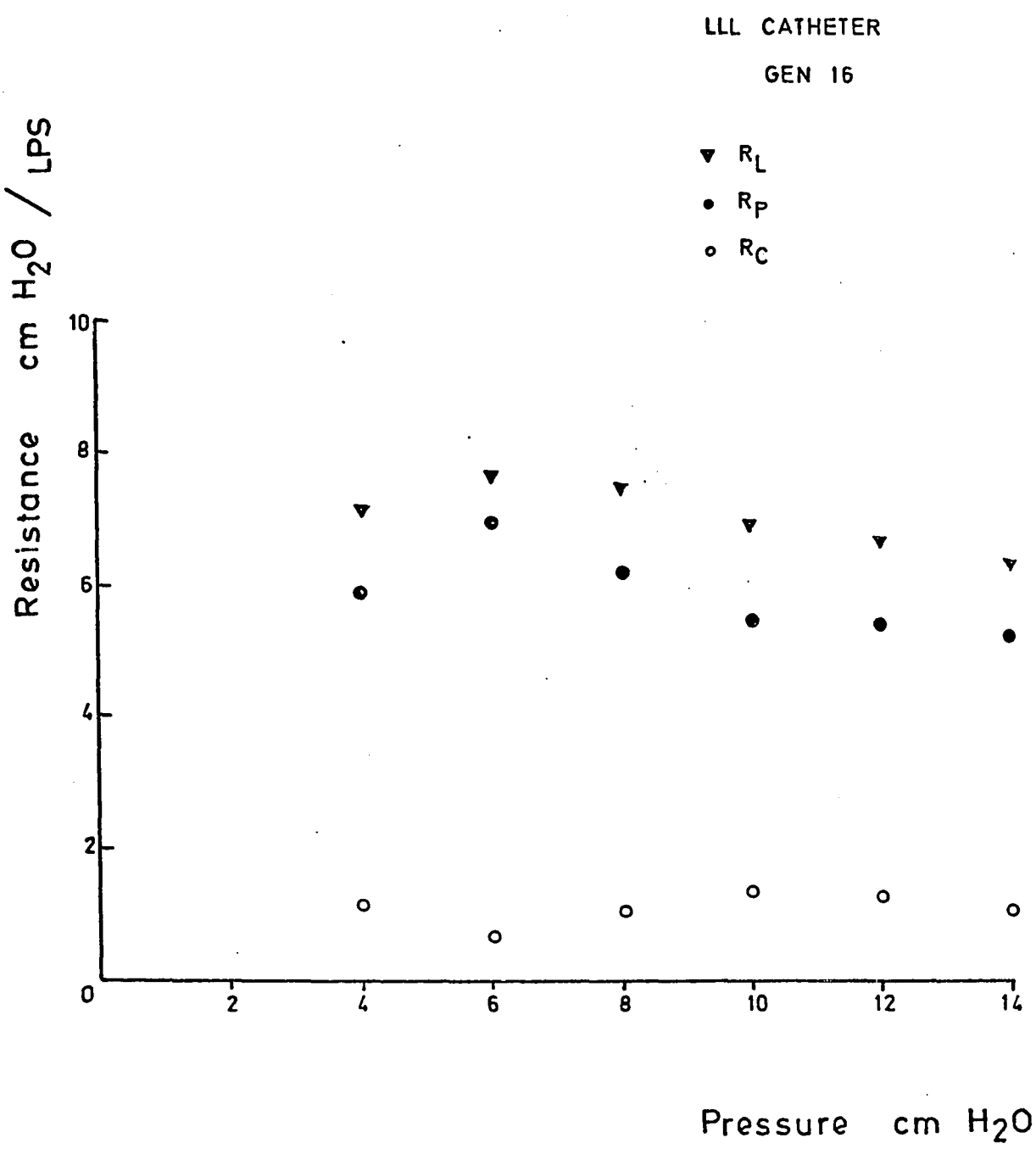

LLL CATHETER
GEN 16
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
10
2
4
6
8
10
12
14
Pressure cm H_2O

Fig. 26 Dog 18

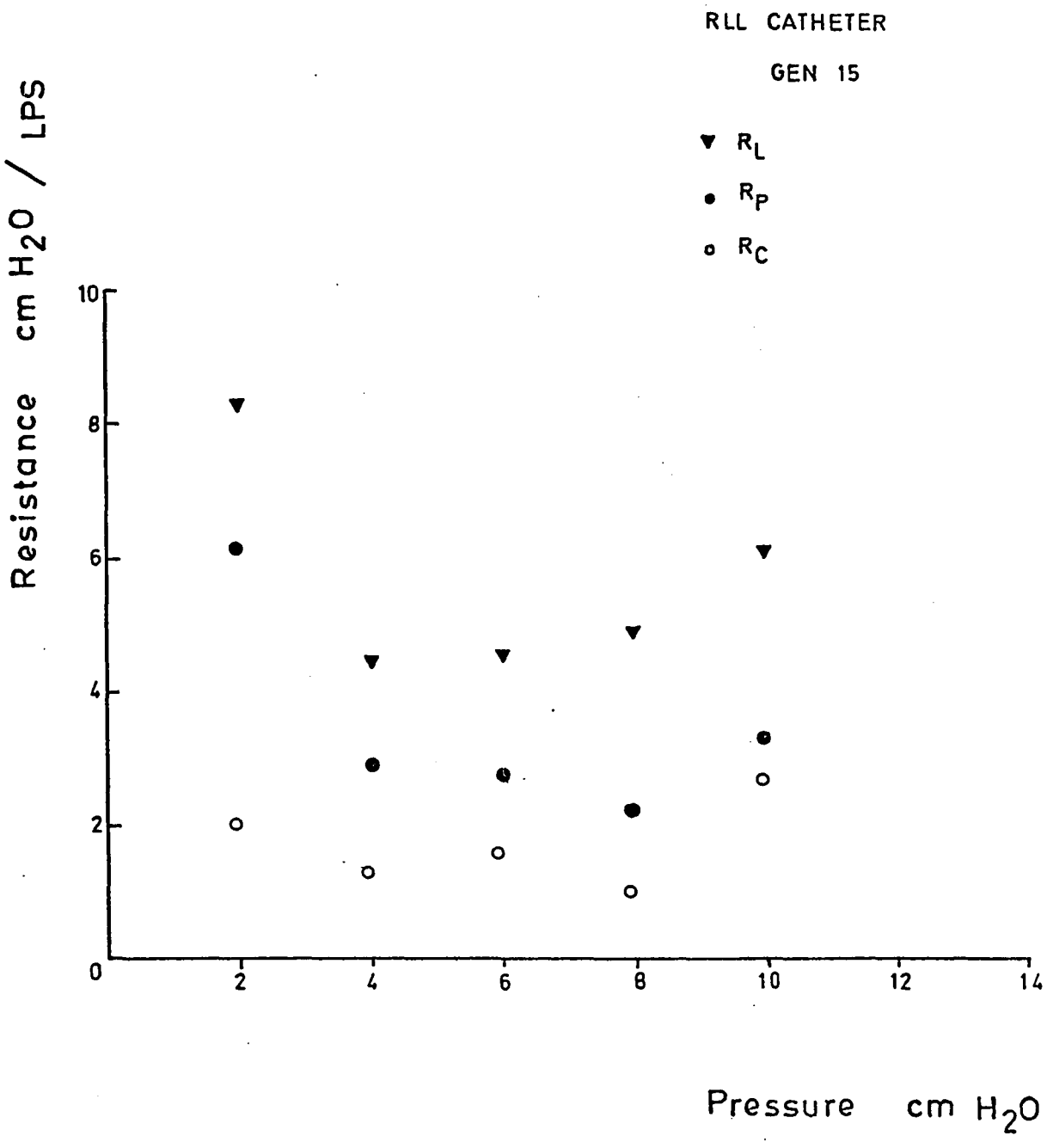

RLL CATHETER
GEN 15
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
10
2
4
6
8
10
12
14
Pressure cm H_2O

Fig.27 Dog 19

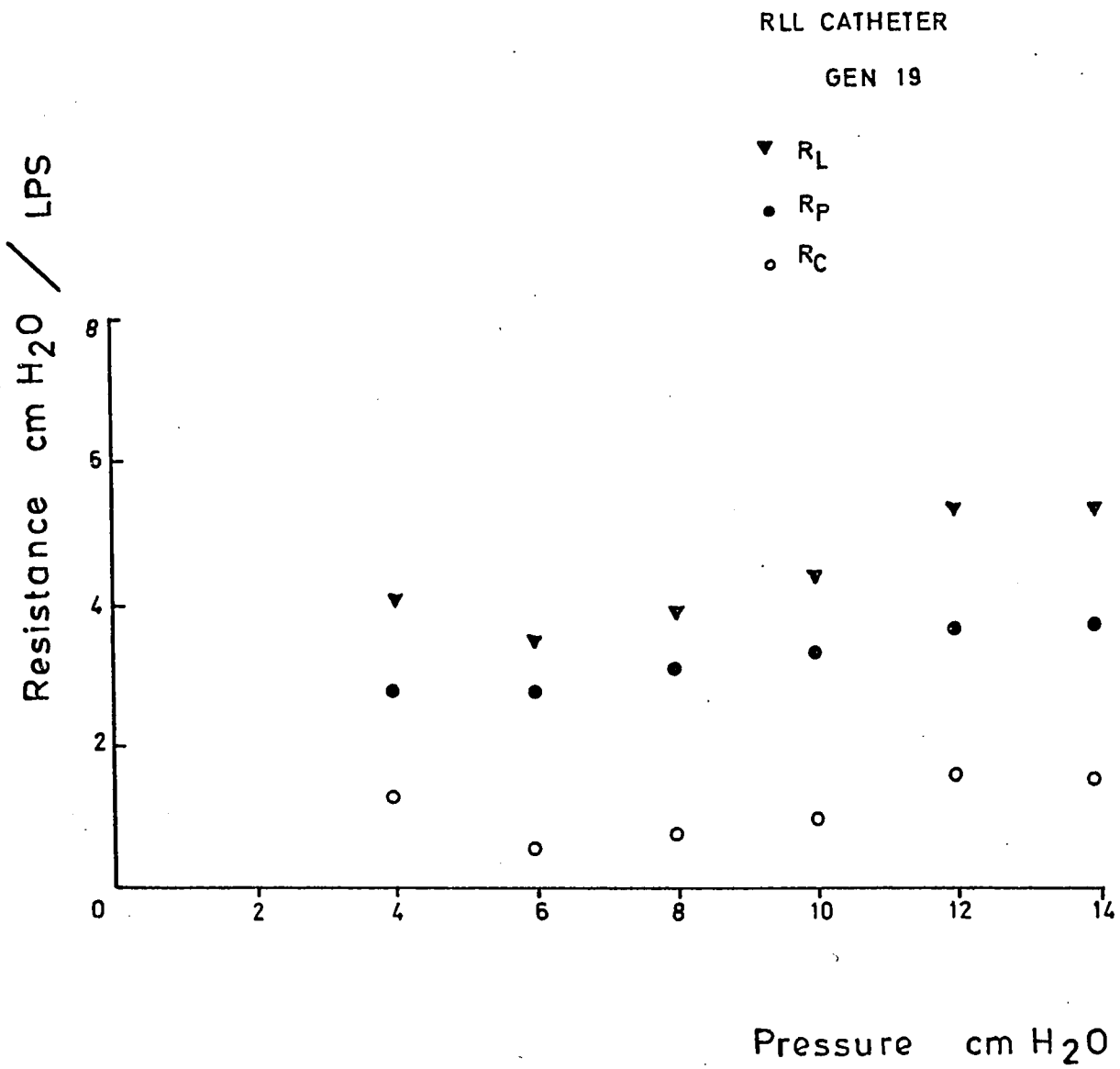
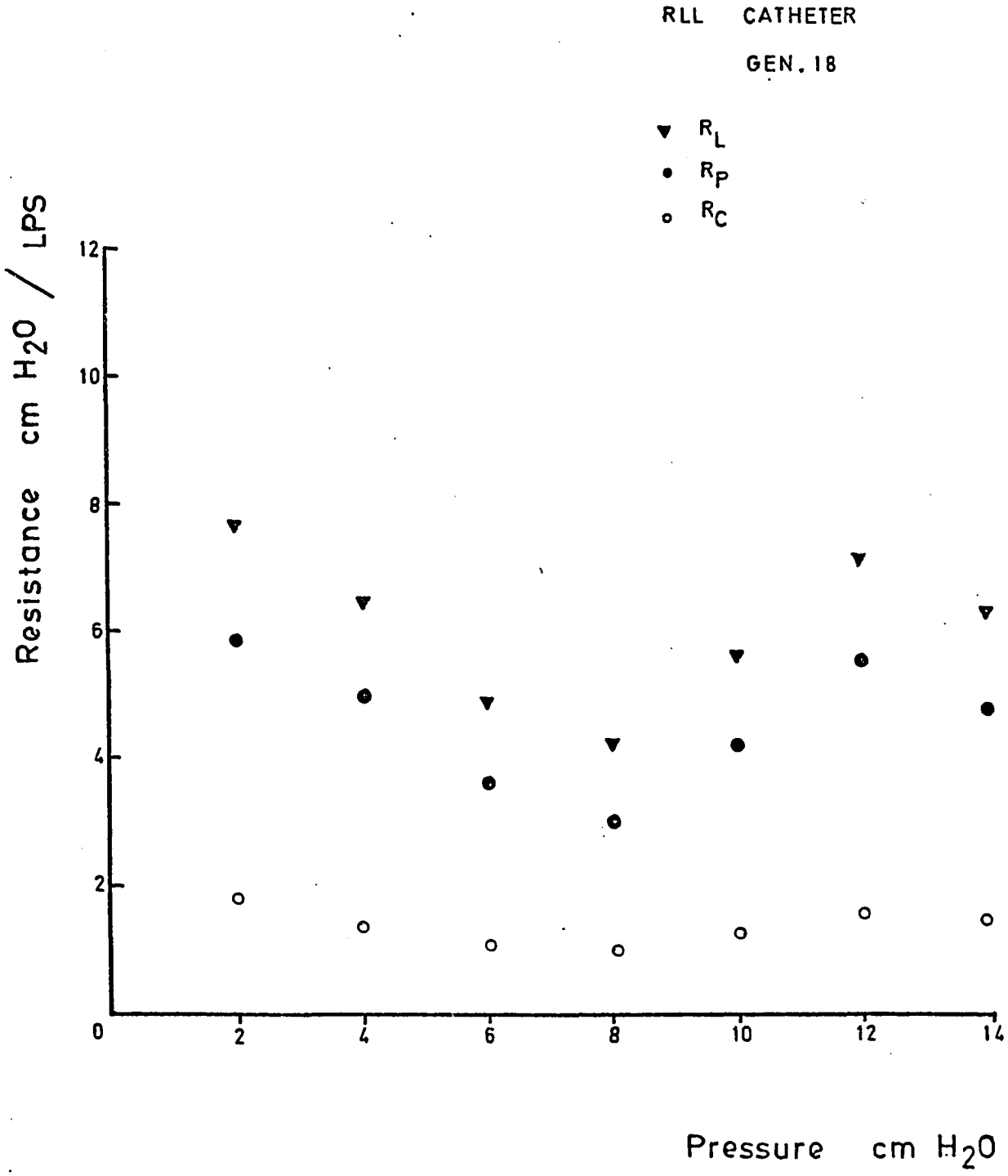
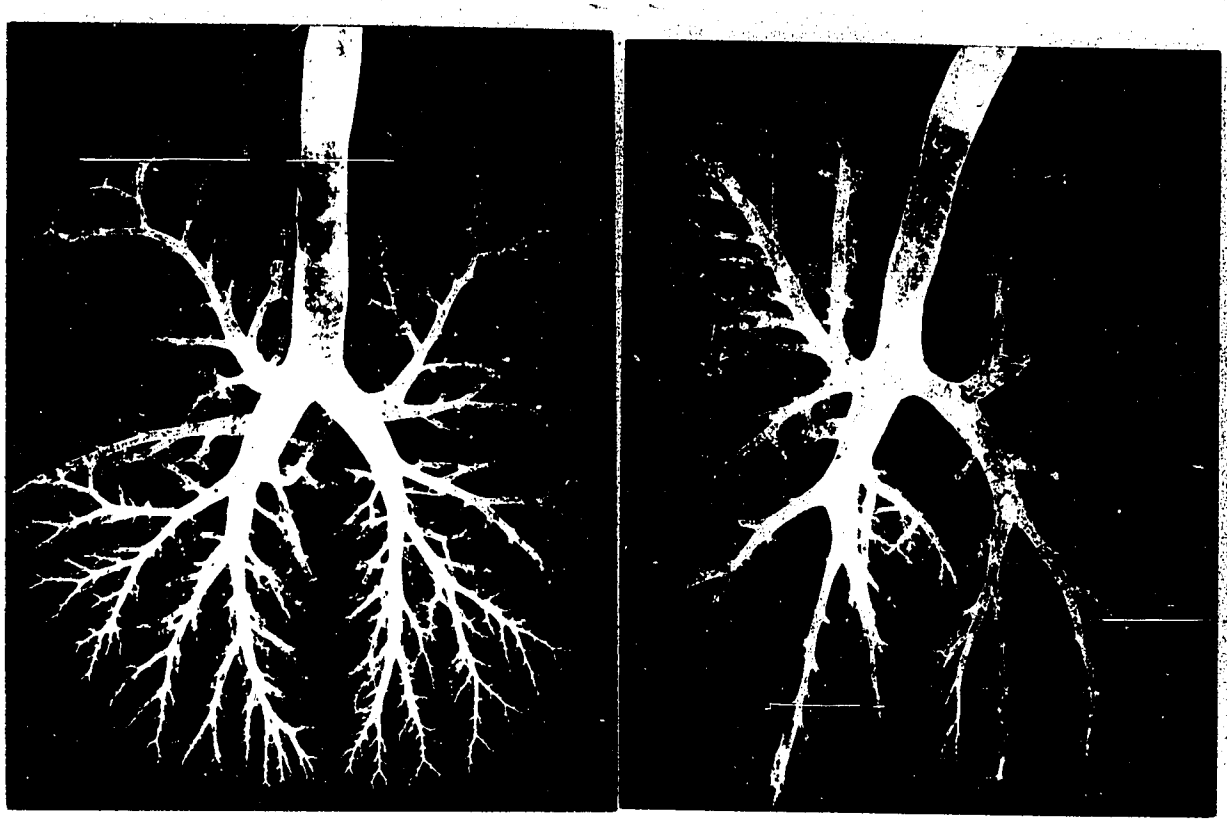

RLL CATHETER
GEN 19
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
0
2
4
6
8
10
12
14
Pressure cm H_2O

Fig.28 Dog 20


RLL CATHETER
GEN. 18
R_L
R_P
R_C
Resistance cm H_2O / LPS
0
2
4
6
8
10
12
14
Pressure cm H_2O

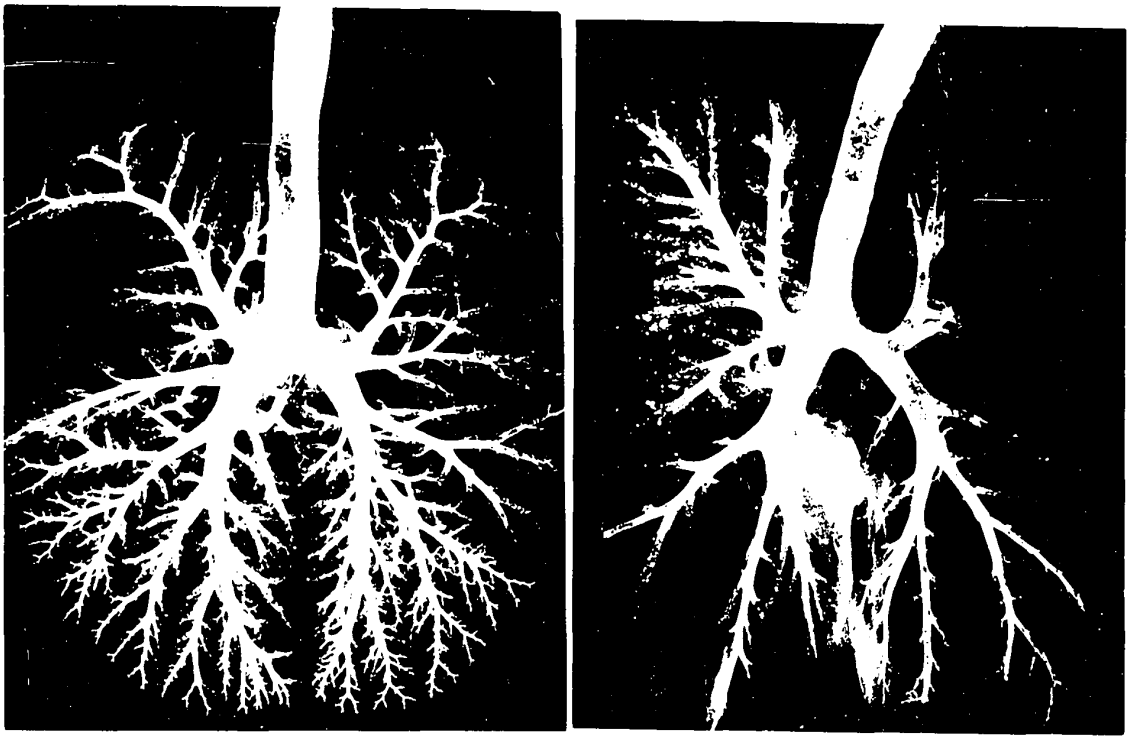


(A) (B)

Fig. 29. Post-Mortem Bronchograms.

(A) Showing normal contrast material outlining the bronchial tree. The bronchial outlines were smooth, tapering and evenly filled.

(B) The upper lobe bronchi show loss of normal tapering. Many of small airways appear occluded with blunt and tapering ends. (Both x-rays taken at the same distending pressure of 20 cm H_2O).



(A) (B)

Fig. 29. Post-Mortem Bronchograms.

(A) Showing normal contrast material outlining the bronchial tree. The bronchial outlines were smooth, tapering and evenly filled.

(B) The upper lobe bronchi show loss of normal tapering. Many of small airways appear occluded with blunt and tapering ends. (Both x-rays taken at the same distending pressure of 20 cm H_2O).

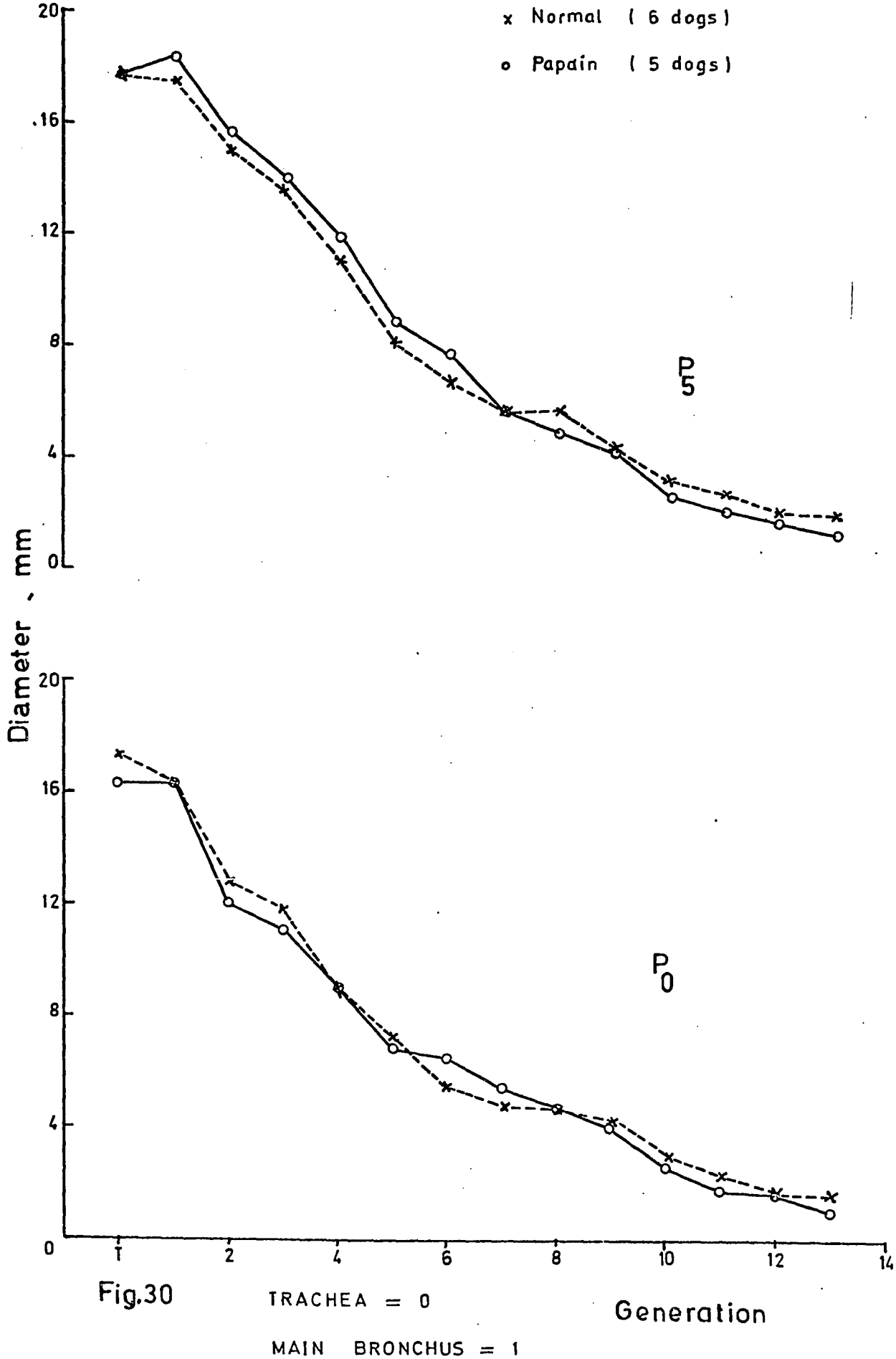


Fig.30 TRACHEA = 0

MAIN BRONCHUS = 1

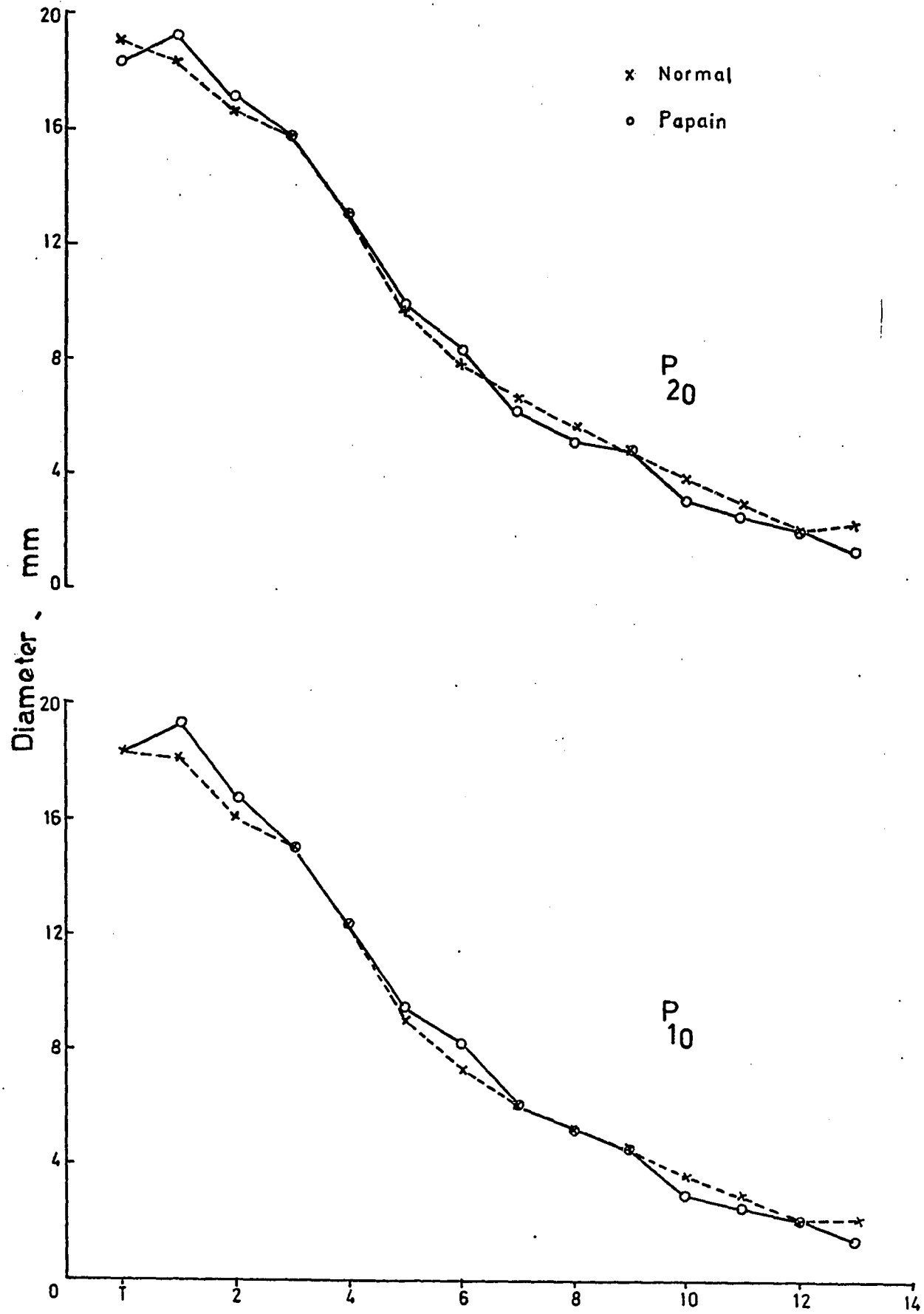


Fig. 30 TRACHEA = 0

MAIN BRONCHUS = 1

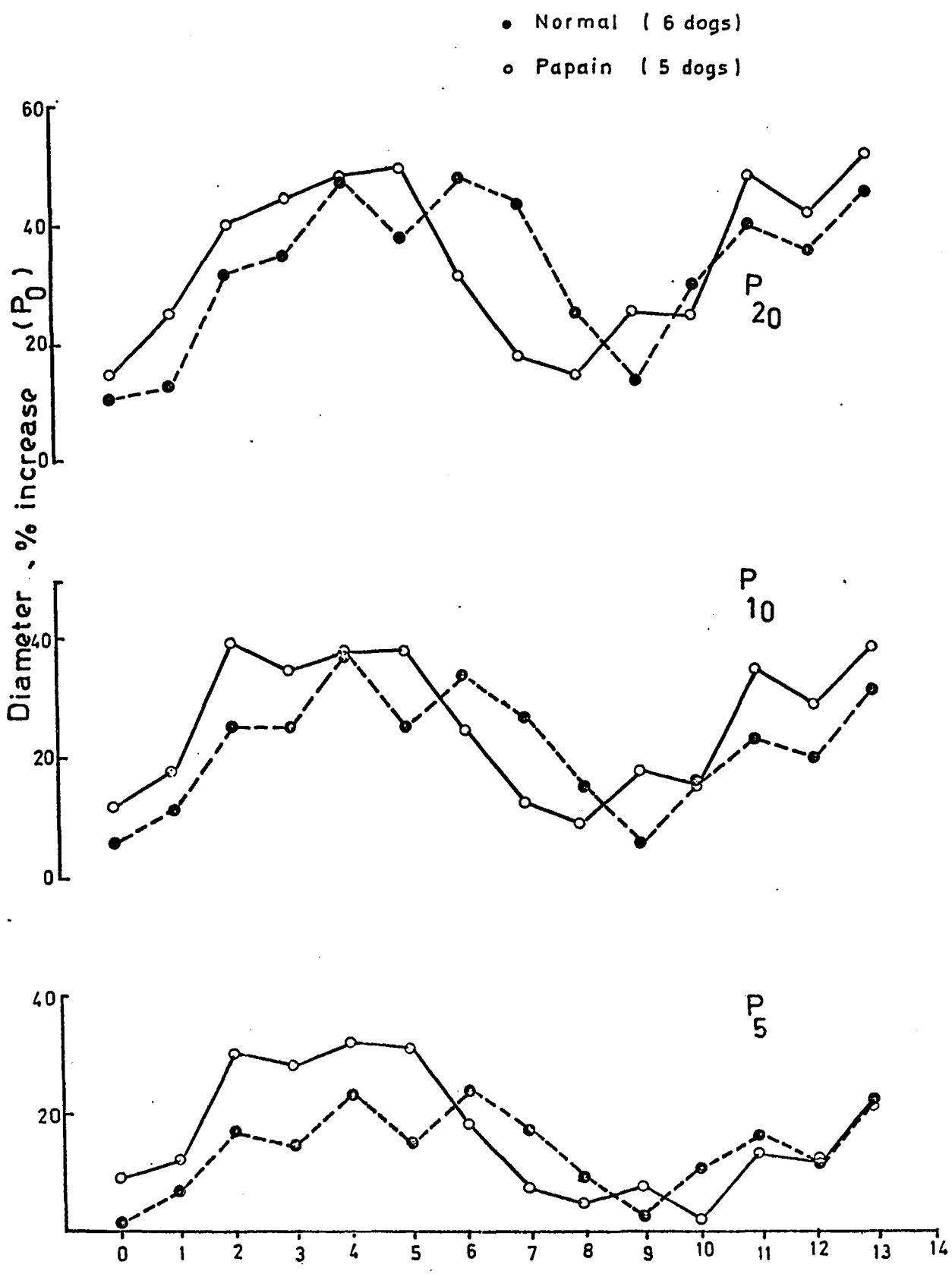


Fig. 31 TRACHEA = 0

MAIN BRONCHUS = 1

Tracheo-Bronchial Diameter

Absolute diameters of the tracheas and bronchi were averaged and the mean values were plotted against generations. The control and experimental values were compared at various distending pressures and are shown in Figs.30 and 31.

As shown, the diameters of small airways (distal to the sixth generation) in emphysema were smaller than in the controls while the upper airways were larger. This may reflect the loss of radial traction of the small bronchi due to destruction of lung parenchyma or due to intrinsic narrowing.

At a lower distending pressure (P_5) the peripheral airways of the emphysematous lung showed a smaller increase in diameters than the normal ones did. However, at a higher distending (P_{20}) pressure the changes were reversed. These results indicate that in emphysema the peripheral airways were narrowed and stiff at a lower lung volume but at a higher lung volume or when an adequate pressure was applied, they exhibited hypercompliance.

Pathological Studies

The morphological data are summarized and presented in Table VII.

Gross Findings (Fig.32-37)

On post-mortem examination, the striking feature was that the lungs of dog 20 had no tendency to completely collapse when removed

TABLE VII

Morphologic Studies

Normal Dogs

Dog No.	Weight (lb)	TLV (liters)	Point Count	Lm, (mm)	ISA, (M^2)	ISA_2, (M^2)
1	44	2.43	0	0.106	79	69
2	45	2.10	0	0.098	73	71
3	42	2.20	0	0.110	71	67
4	45	2.53	0	0.116	78	67
5	30	1.81	0	0.122	55	59
6	61	4.00	0	0.149	98	62
7	60	3.09	0	0.132	82	61
			Mean ± SD	*0.119±0.017		**65±4

Emphysematous Dogs

9	48	1.48	0	0.165	32	39
10	49	1.60	0	0.144	41	48
11	24	1.72	0	0.176	36	36
13	27	1.17	0	0.124	35	39
15	27	1.51	0	0.140	37	41
16	69	2.40	0	0.140	66	57
17	50	2.88	1	0.150	69	34
18	45	2.12	0	0.138	54	52
19	44	2.21	1	0.152	59	56
20	48	3.21	17.7	0.258	46	33
			Mean ± SD	*0.159±0.04		**47±9

TLV = total lung volume, measured by water displacement.

% of parenchyma involved calculated by use of point counting method.

Lm = mean linear intercept

ISA = internal surface area at TLV

ISA_2 = internal surface area at a lung volume of 5 liters

* significant difference P = 0.01

** significant difference P ≈0.001

from the thorax. This was an indication of air trapping in the lungs. Since the lung volume of this dog had not been measured during life (the dog died before physiological studies were completed), the post-mortem residual volume was measured on this dog by means of water displacement. The difference between the volumes of the lung containing residual air and during the gas-free stage is the volume of gas trapped in the lung. The residual volume obtained by this means was 940 ml. which in normal dogs of the same weight was 245 and 305 ml. It therefore shows a large increase in the residual volume. In dogs 17 and 19, the evidence of air retention was also observed but it was only to a small degree and was absent in the remaining dogs.

Varying amounts of panlobular emphysema were found in all dogs, except dogs 10 and 13 where no emphysema was recognized (the examples of the lesion are shown in fig.33-37). The lungs of dog 9 showed quite extensive dilatation of the alveolar ducts. In dogs 11, 15-18, the emphysematous lesions were patchy and of variable severity and there were areas where emphysema occurred immediately adjacent to normal lung parenchyma (fig. 35).

Dog 19 (fig. 36) showed generalized mild panlobular emphysema of the left lung but relatively little emphysema was present in the right lung. Dog 20 (fig. 37) displayed the worst emphysema in the series. Both lungs showed diffuse mild to moderate degrees of emphysema involvement. The left middle lobe was consolidated and there were bronchiectatic changes. The cut surface of the lung showed

protrusion of the bronchi and blood vessels while the parenchyma fell away.

Histological Studies

In general, there was a loss of the normal sharp distinction between the size and shape of multifaceted alveoli and the larger, rounded or tabular ducts on respiratory bronchioles (fig. 42). The results were effacement of the normal peripheral lung structure with departitioning and formation of large air spaces which consisted of enlarged, flattened and often confluent alveoli, alveolar sacs and alveolar ducts (Fig. 43,44). The lesion seen in dog 9 was similarly observed on gross examination. There was predominant dilatation of the alveolar ducts and sacs (Fig. 42) with a mild degree of destruction of the alveolar walls. In dogs 10 and 13 the usual histology sections and paper mounted whole lung sections showed no striking abnormality. However, thick sections (50-100 μ) definitely showed differences when they were compared to the controls (Fig. 41). The lungs of dogs 11, 15 and 16 showed focal emphysema and duct ectasia. A small hemorrhagic area was observed in dog 11. Emphysema was scattered throughout normal sections of dogs 17, 18 and 19. Interstitial inflammation and mild pulmonary edema were additional features in these dogs. Small areas of focal fibrosis and mild bronchiolitis were observed in dogs 17 and 19.

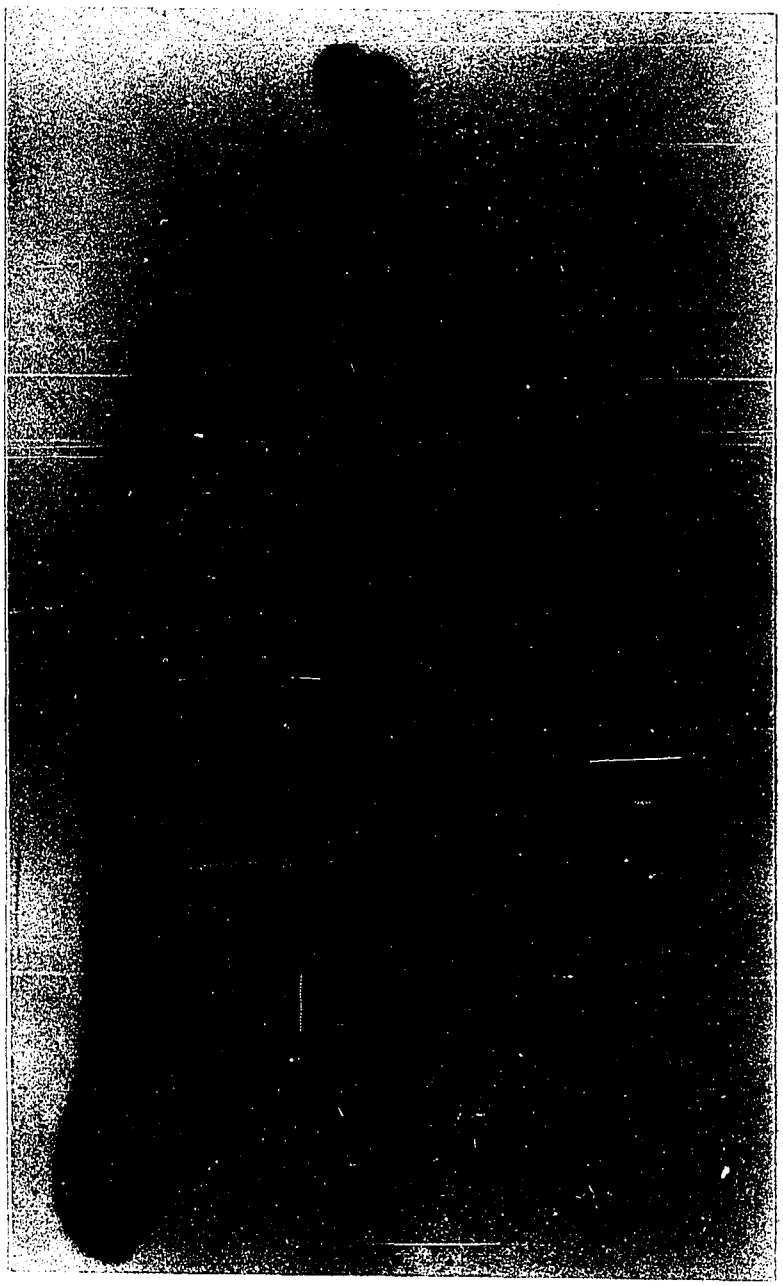


Fig. 32. Paper mounted whole lung section showing normal lung.

Fig. 32. Paper mounted whole lung section showing normal lung.

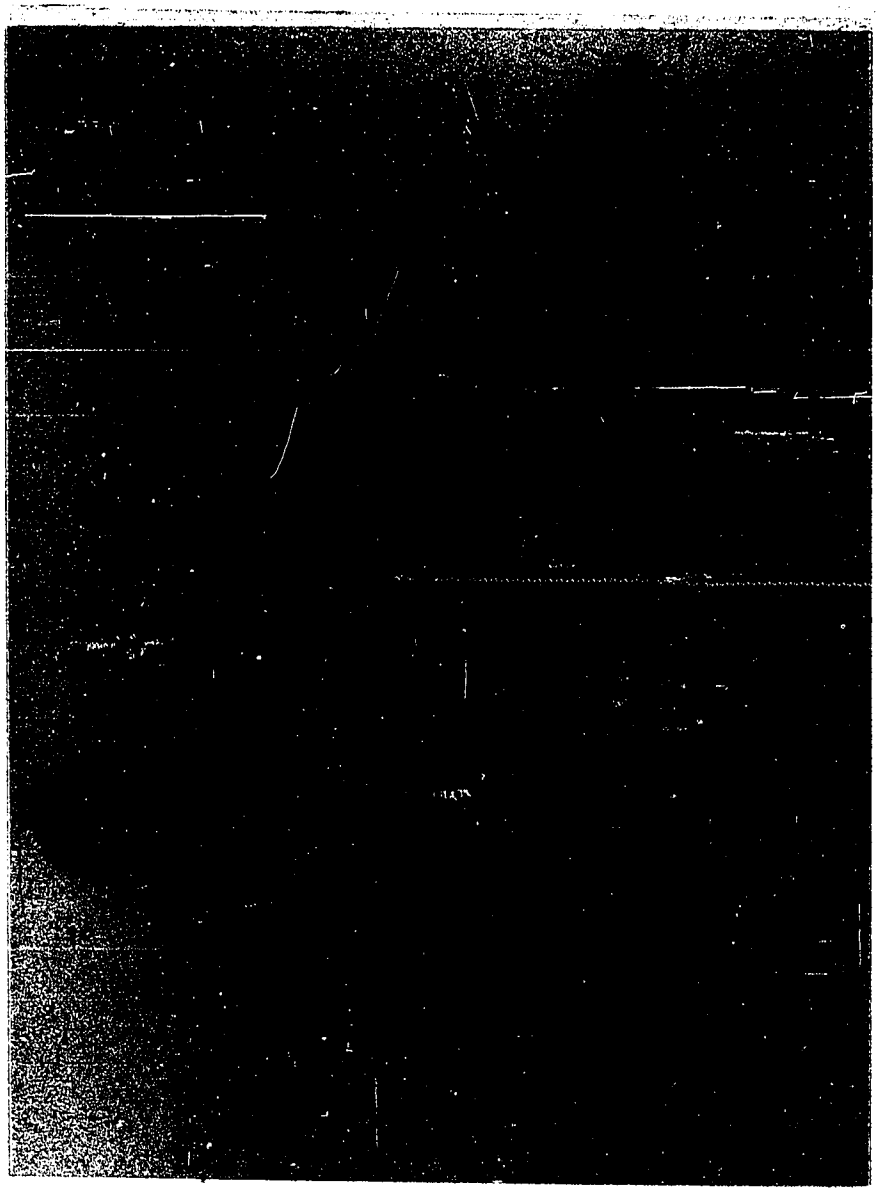


Fig. 33. Paper mounted whole lung section of mild panlobular emphysema (microscopically identified) which resembles the normal lung.

Fig. 33. Paper mounted whole lung section of mild panlobular emphysema (microscopically identified) which resembles the normal lung.

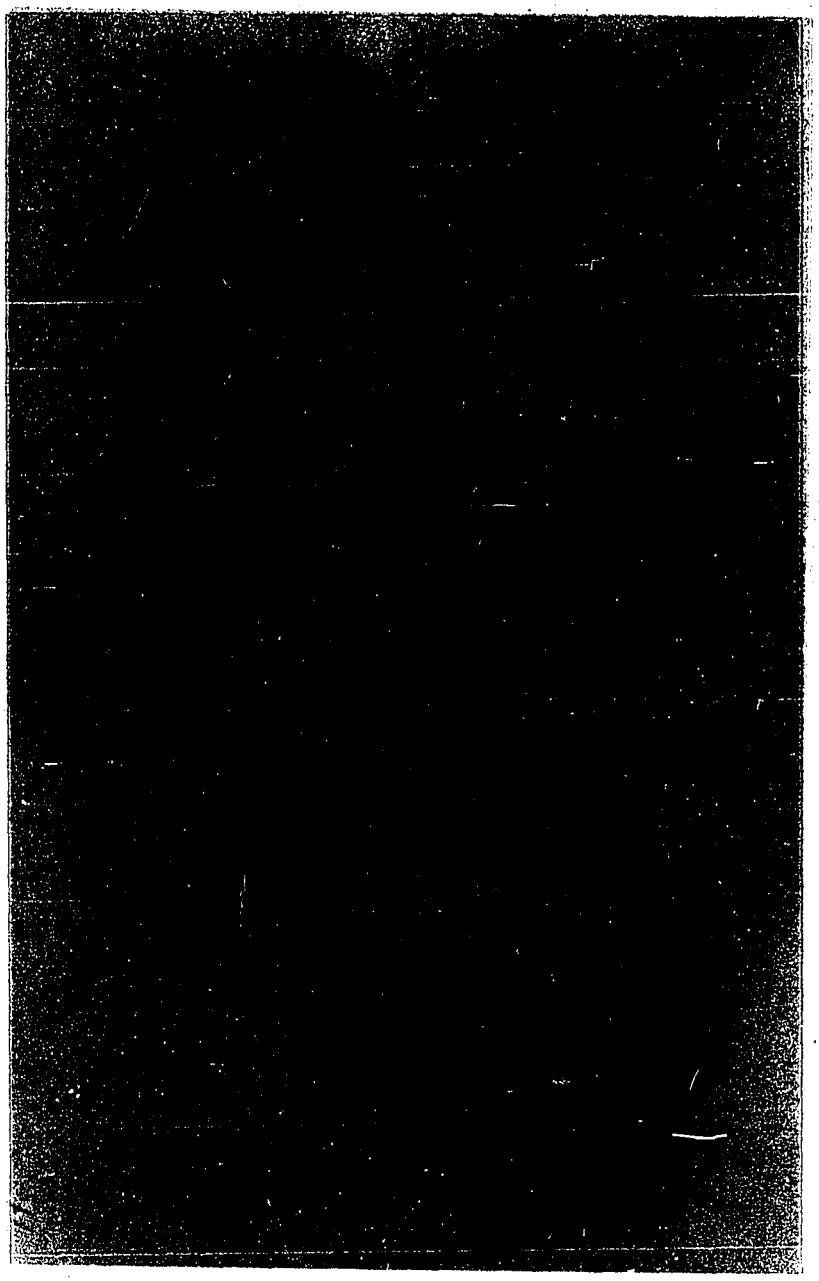


Fig. 34. Paper mounted whole lung section showing mild panlobular emphysema with prominent duct ectasis.

Fig. 34. Paper mounted whole lung section showing mild panlobular emphysema with prominent duct ectasis.

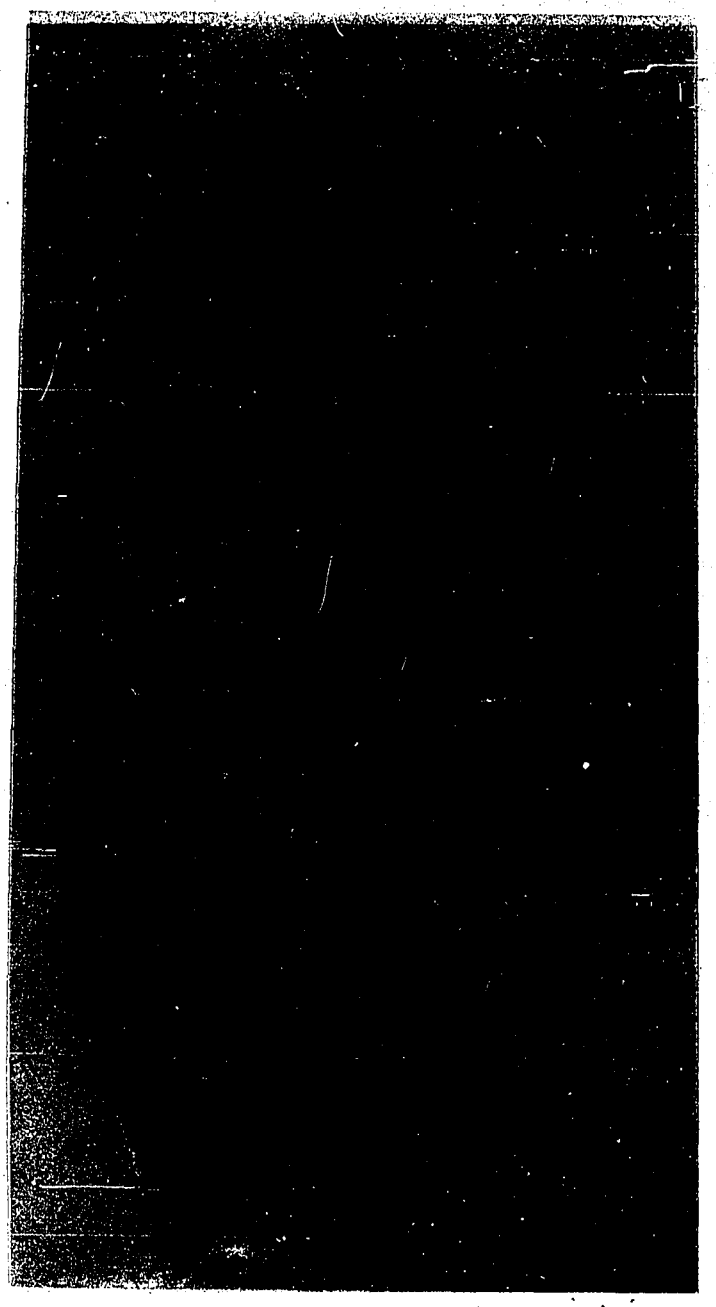


Fig. 35. Paper mounted whole lung section showing mild panlobular emphysema with patchy lesions.

Fig. 35. Paper mounted whole lung section showing mild panlobular emphysema with patchy lesions.

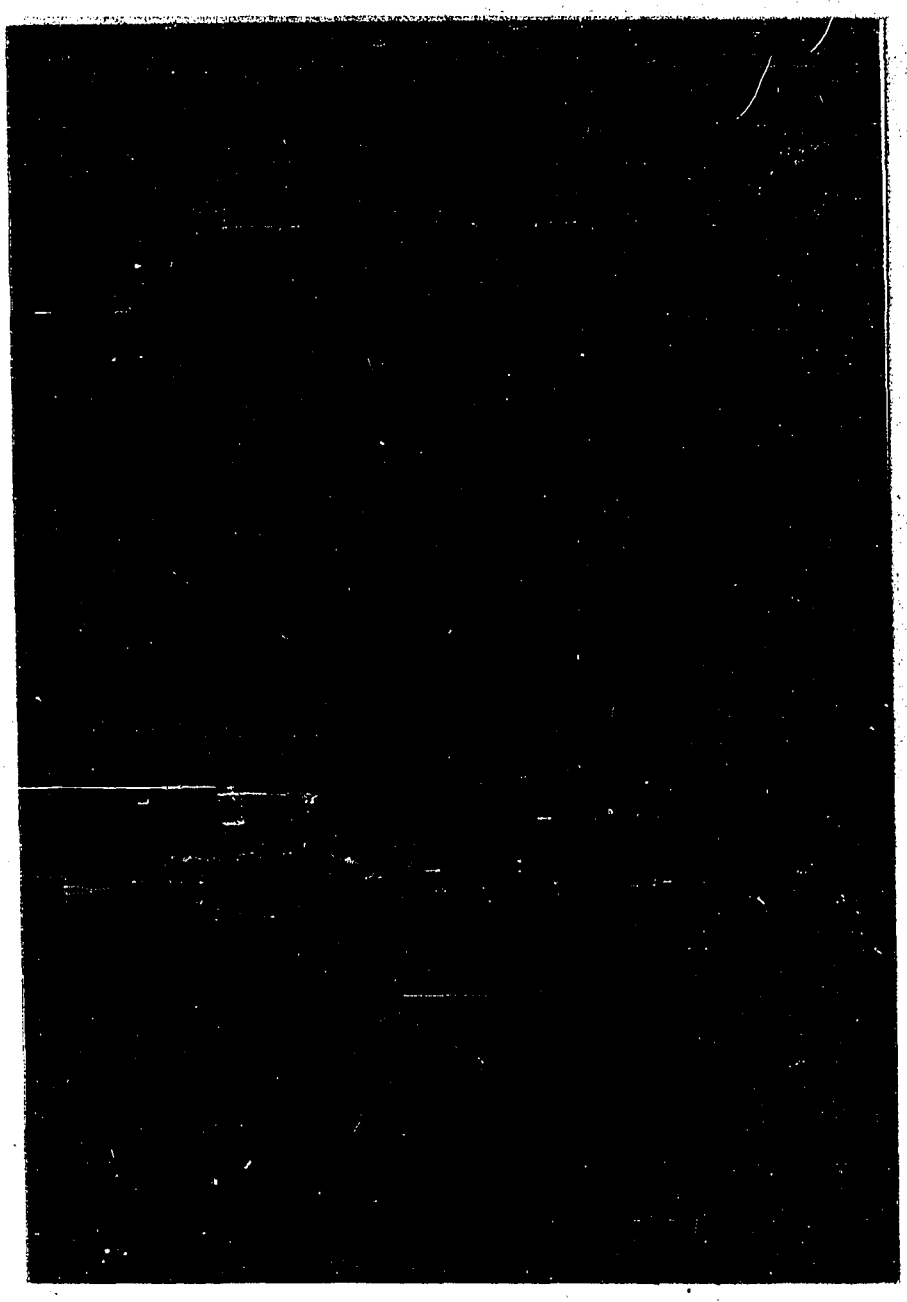


Fig. 36. Paper mounted whole lung section showing moderate panlobular emphysema with diffuse lesions.

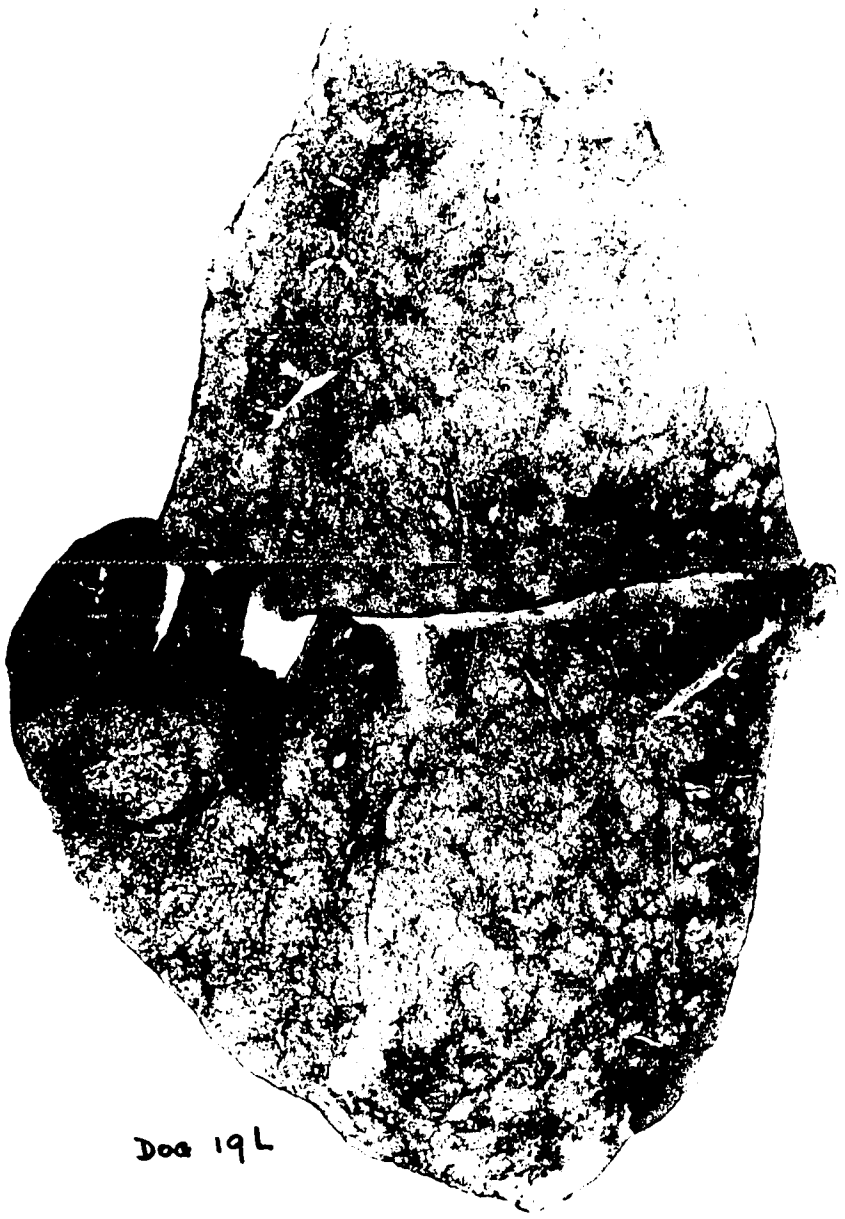


Fig. 36. Paper mounted whole lung section showing moderate panlobular emphysema with diffuse lesions.

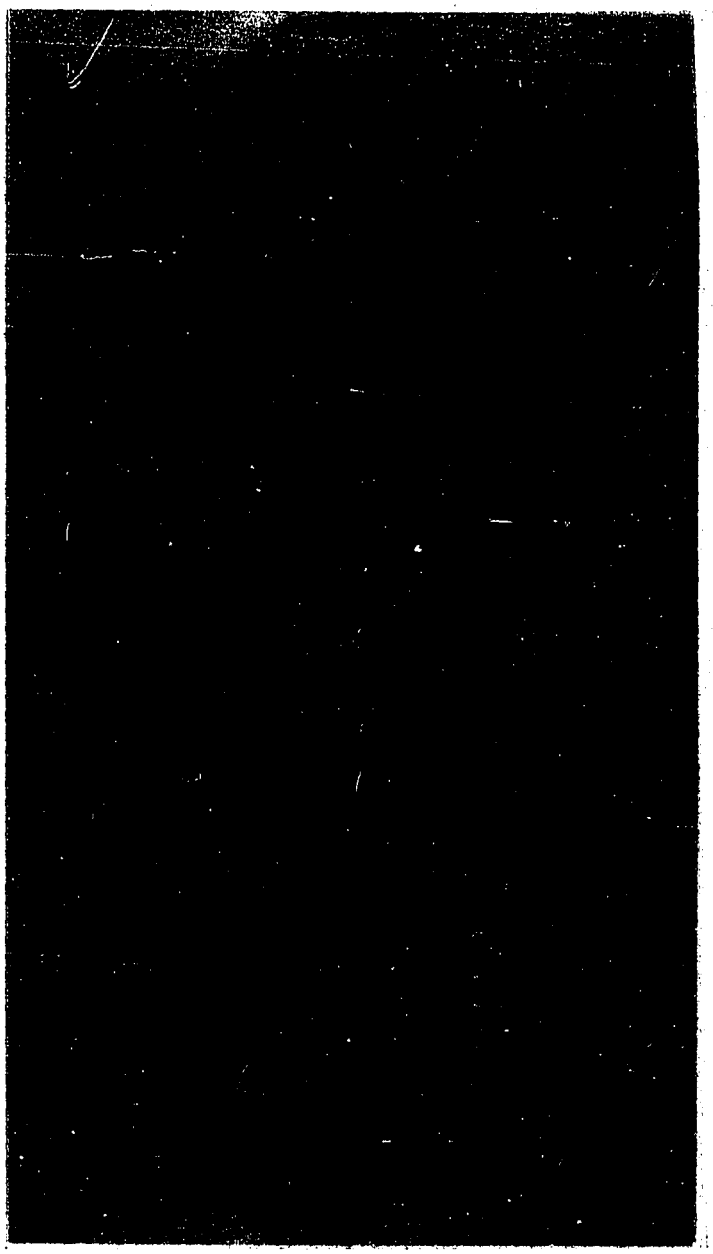


Fig. 37. Paper mounted whole lung section showing moderately severe panlobular emphysema with extensive involvement.

Fig. 37. Paper mounted whol ection showing moderately severe panlobular ma with extensive involvement.

Fig. 38. Photomicrograph of the normal lung as viewed through a dissecting microscope (approx. x 7)

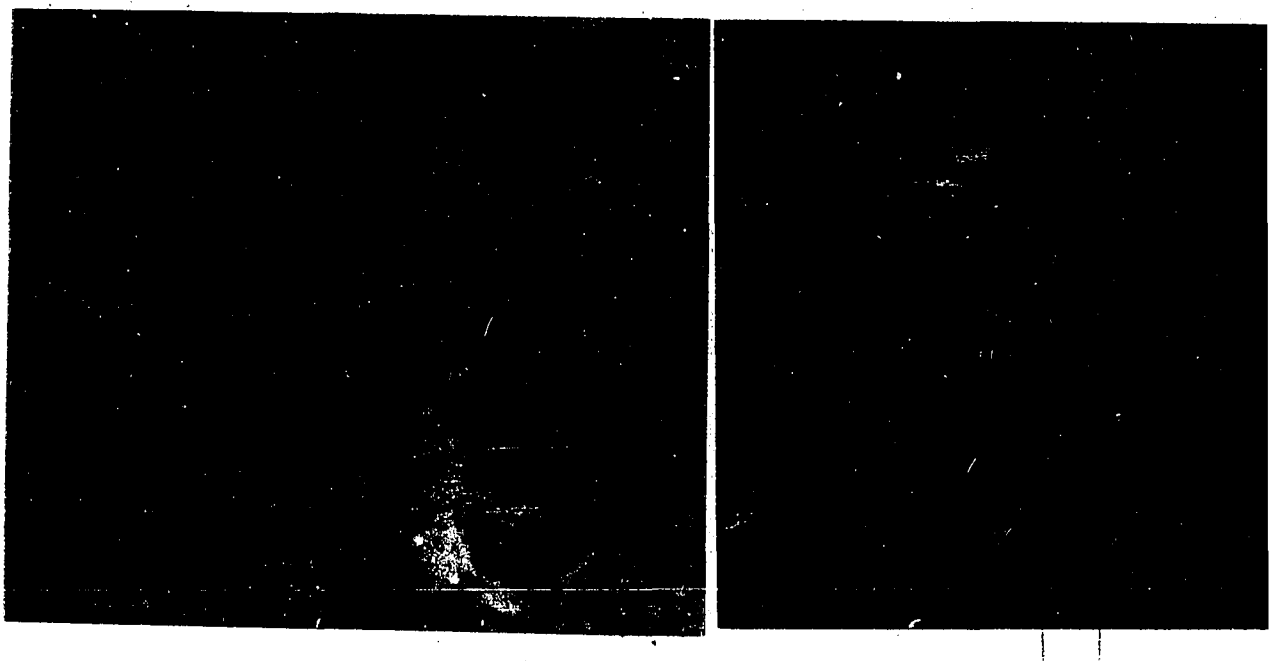


Fig. 39(A) Photomicrograph showing the destruction and dilatation of air spaces in panlobular emphysema, compared with the relatively normal area at the lower left hand corner. (approx. x 7)

(B) Close up the lesion in Fig. 39(A) (approx. x 30)

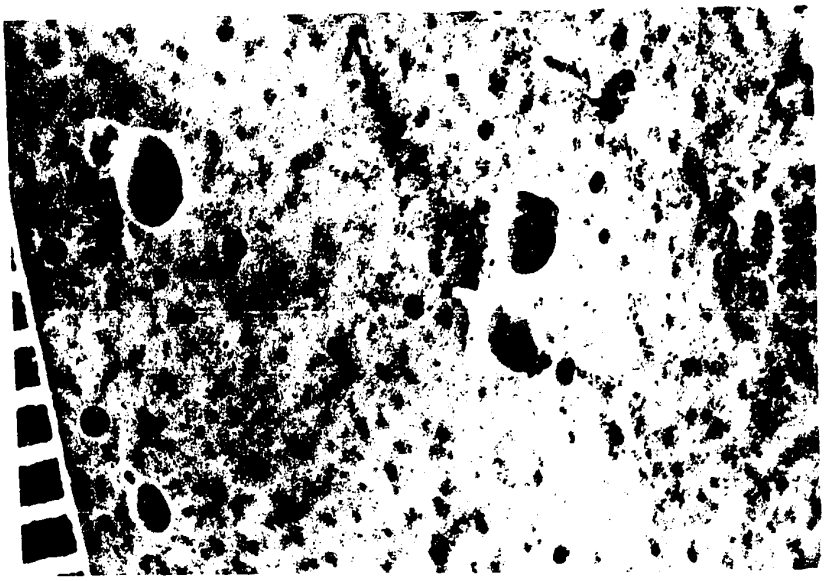


Fig. 38. Photomicrograph of the normal lung as viewed through a dissecting microscope (approx. x 7)

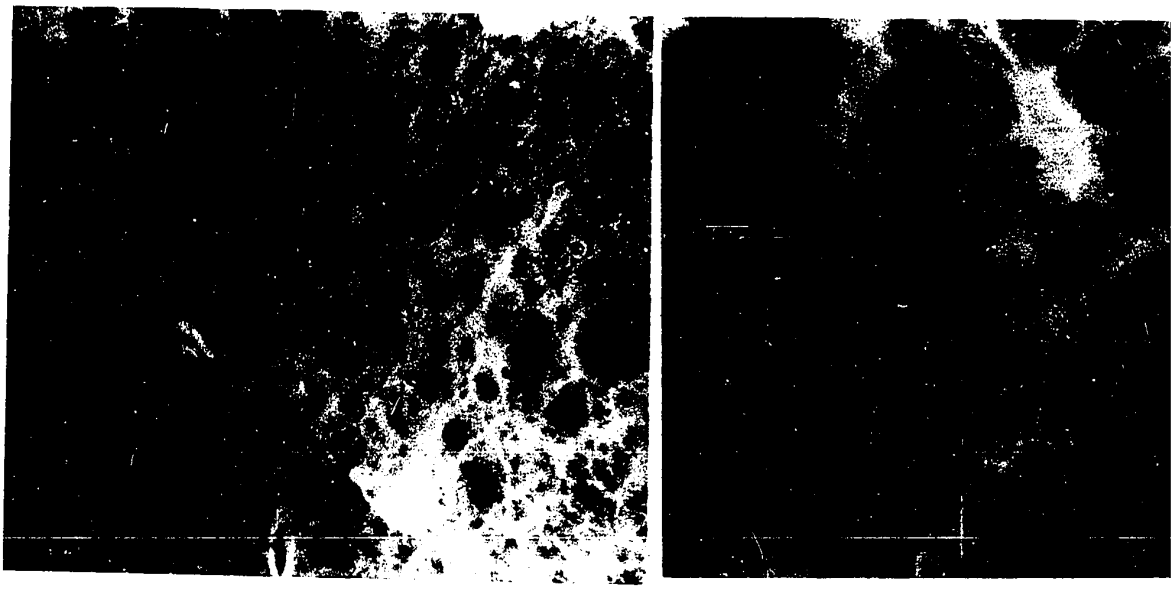


Fig. 39(A) Photomicrograph showing the destruction and dilatation of air spaces in panlobular emphysema, compared with the relatively normal area at the lower left hand corner. (approx. x 7)

(B) Close up the lesion in Fig. 39(A) (approx. x 30)

Fig. 40. Photomicrograph showing moderately severe panlobular emphysema (approx. x 7)

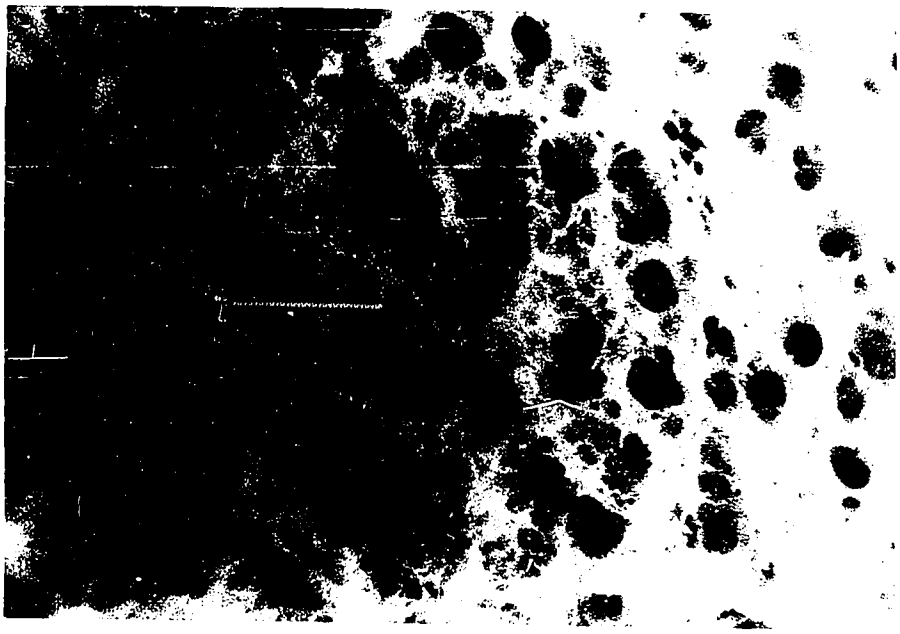


Fig. 40. Photomicrograph showing moderately severe panlobular emphysema (approx. x 7)

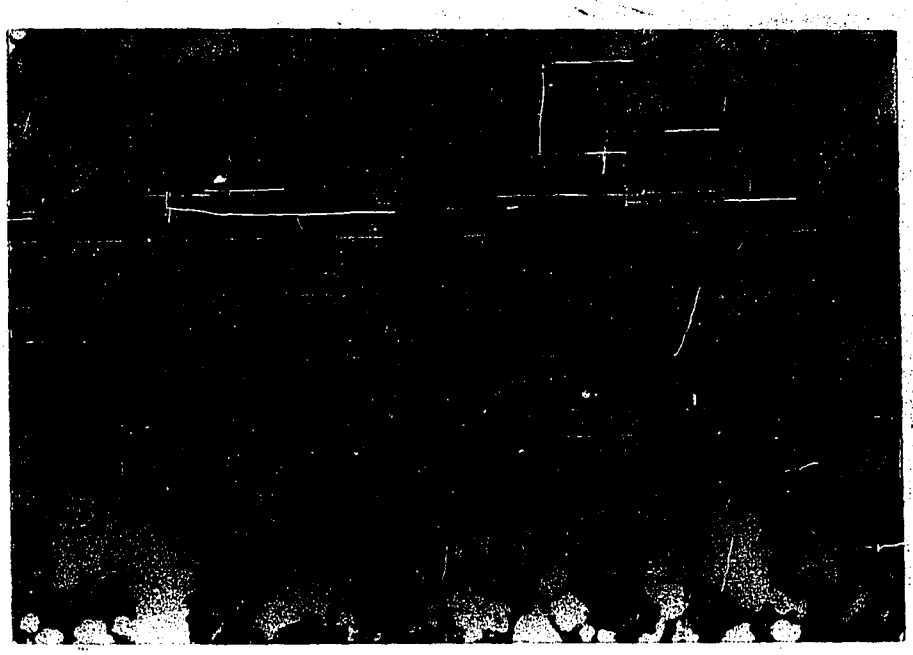


Fig. 41. Normal ducts and alveoli (x 40)

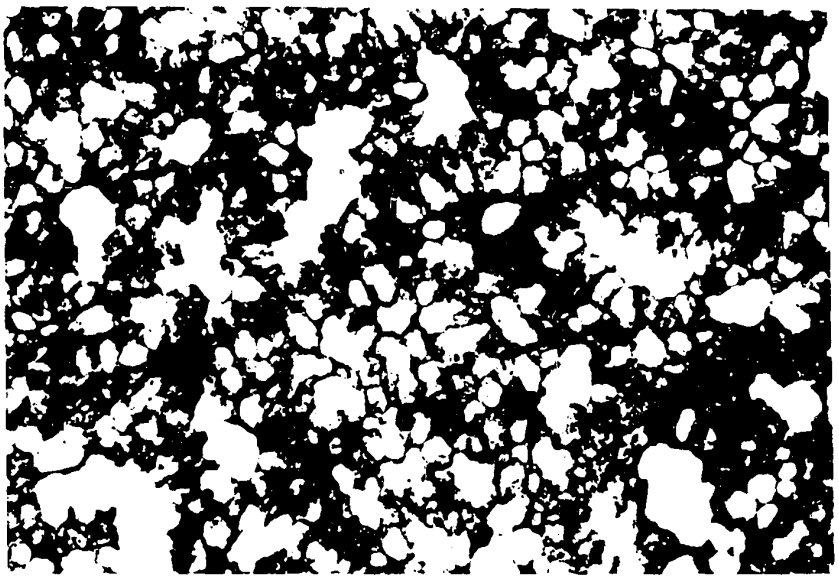


Fig. 41. Normal ducts and alveoli (x 40)

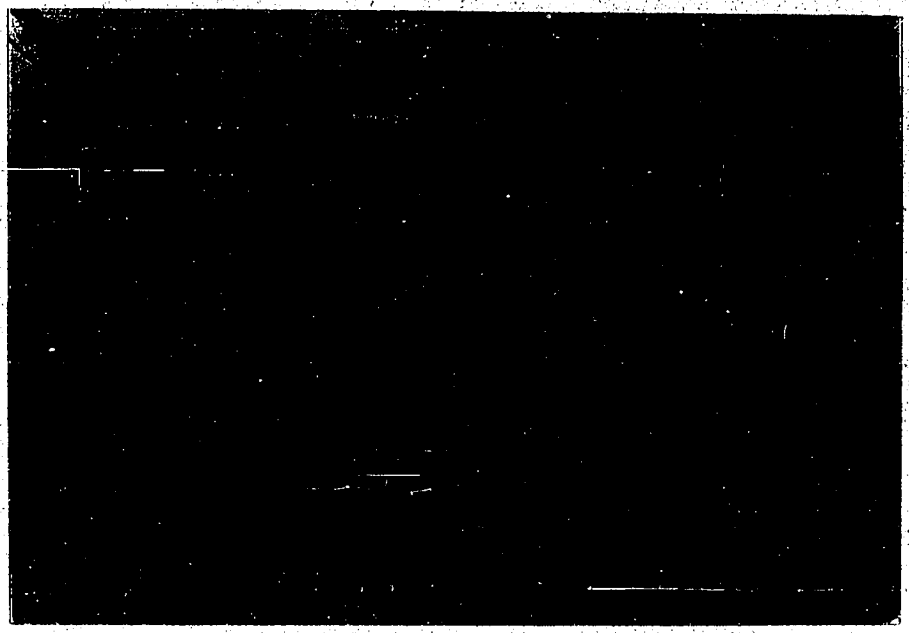


Fig. 42. Showing mild panlobular emphysema with predominant enlargement of alveolar duct and sac (dog 9, x 40)

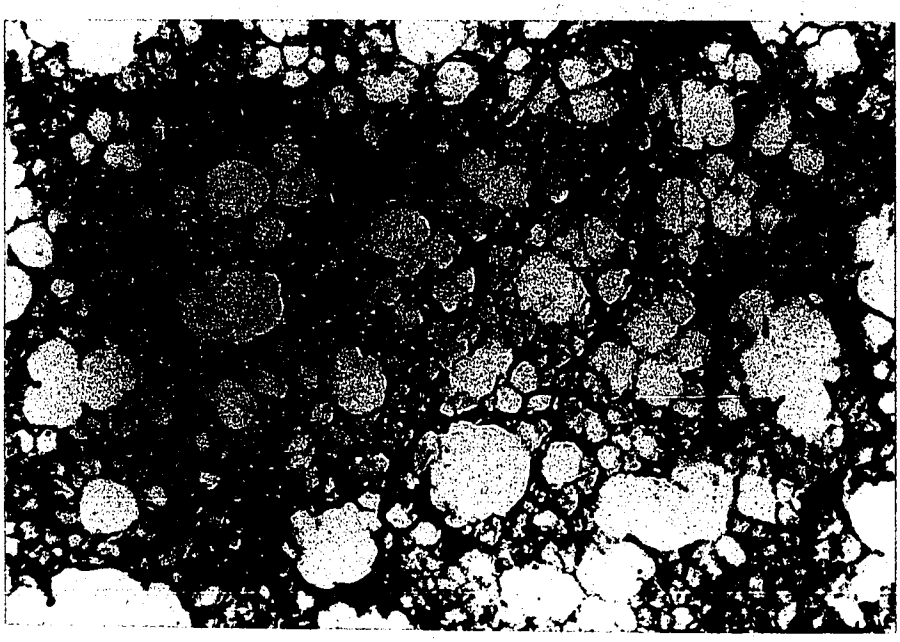


Fig. 43. Mild degree of panlobular emphysema (dog 13, x 40)

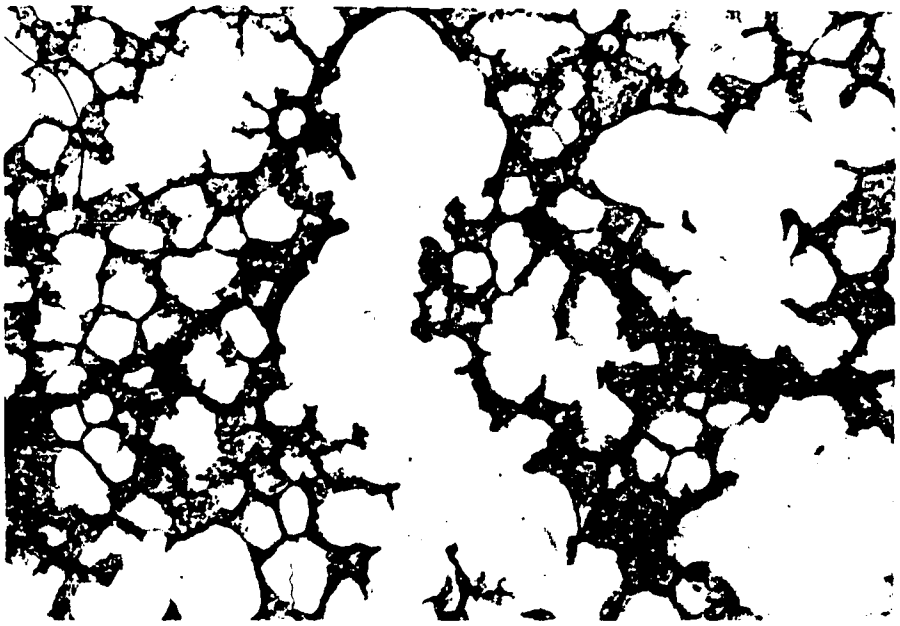


Fig. 42. Showing mild panlobular emphysema with predominant enlargement of alveolar duct and sac (dog 9, x 40)

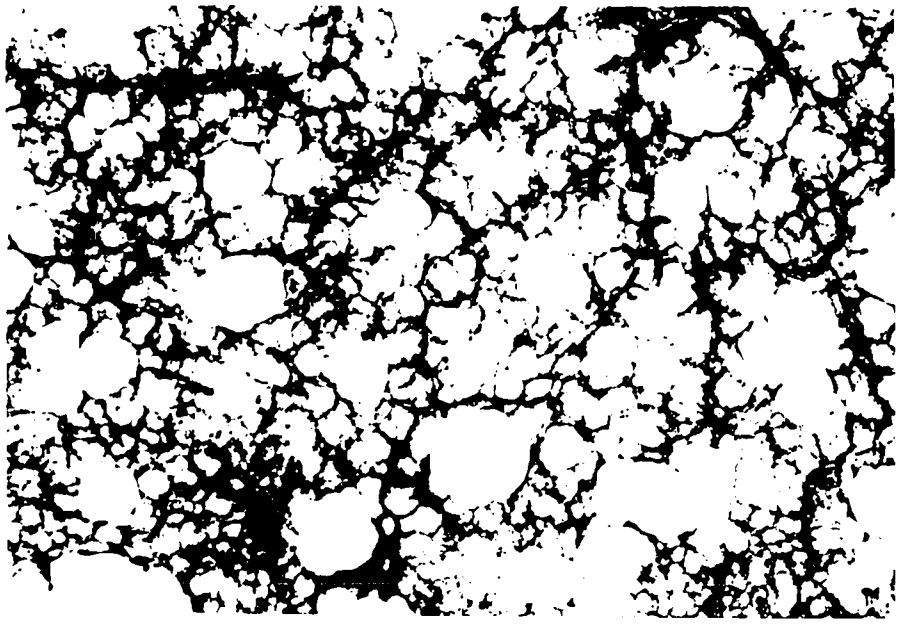


Fig. 43. Mild degree of panlobular emphysema (dog 13, x 40)

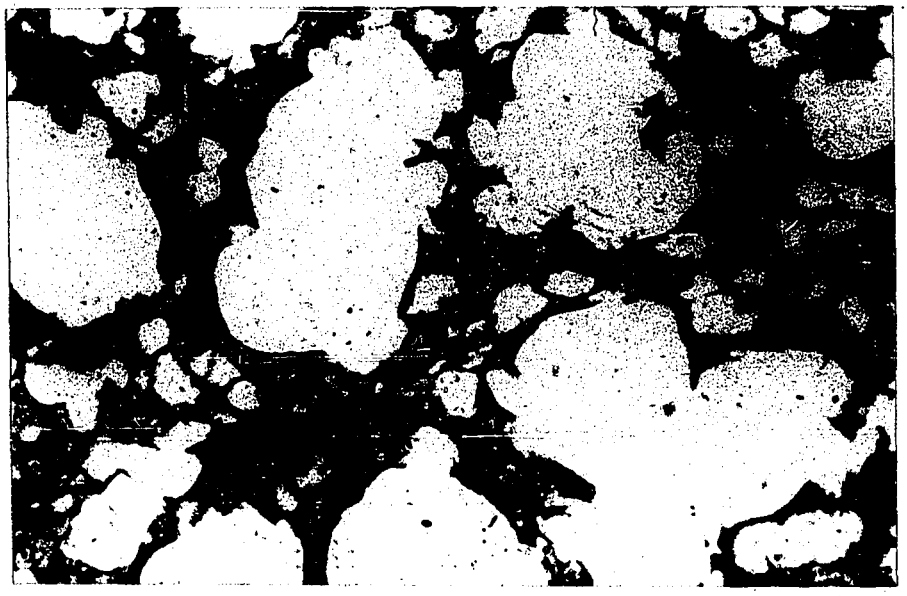


Fig. 44. Moderately severe panlobular emphysema (dog 20, x 40)

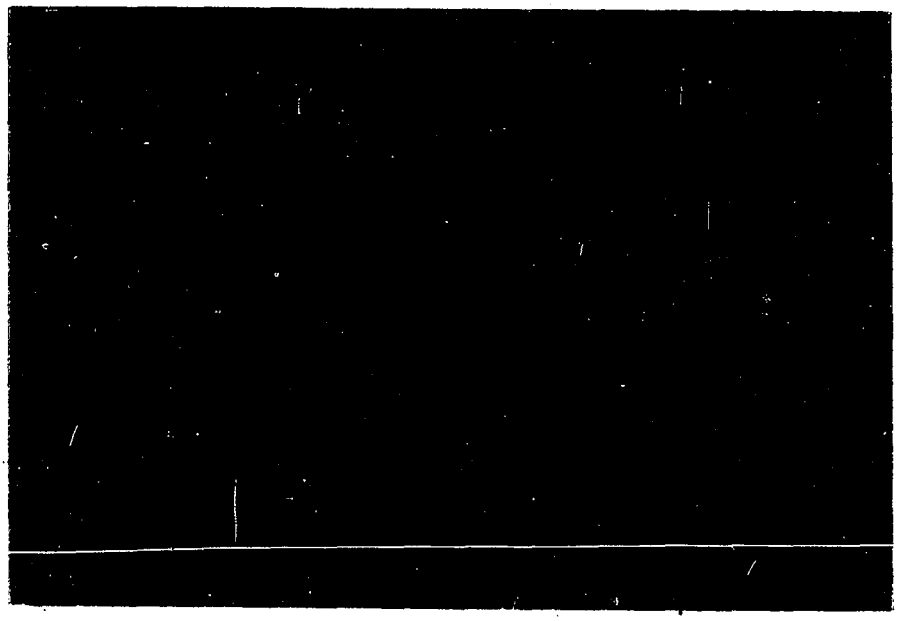


Fig. 45. Photomicrograph of a bronchiole containing an infected mucus plug with inflammation of the surrounding tissues (dog 20, x 100).

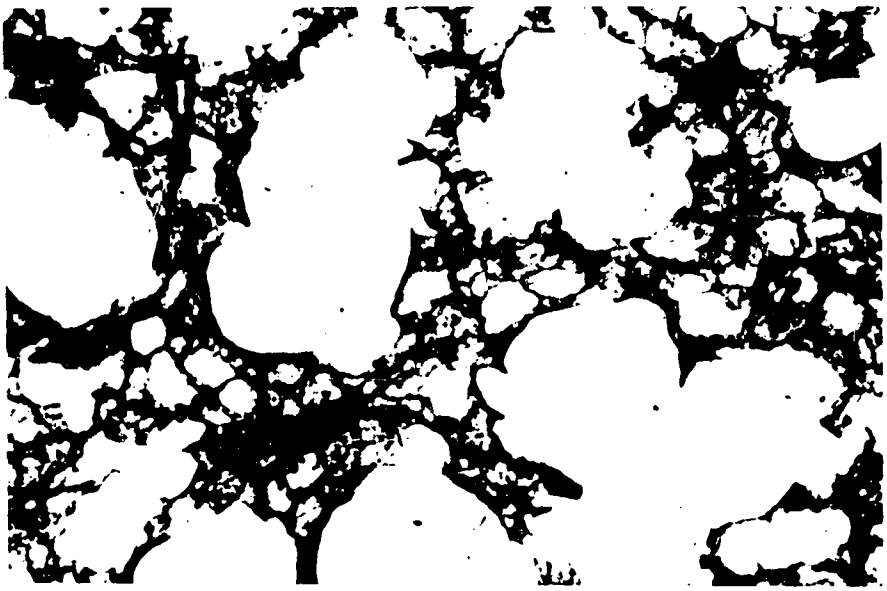


Fig. 44. Moderately severe panlobular emphysema (dog 20, x 40)

Fig. 45. Photomicrograph of a bronchiole containing an infected mucus plug with inflammation of the surrounding tissues (dog 20, x 100).

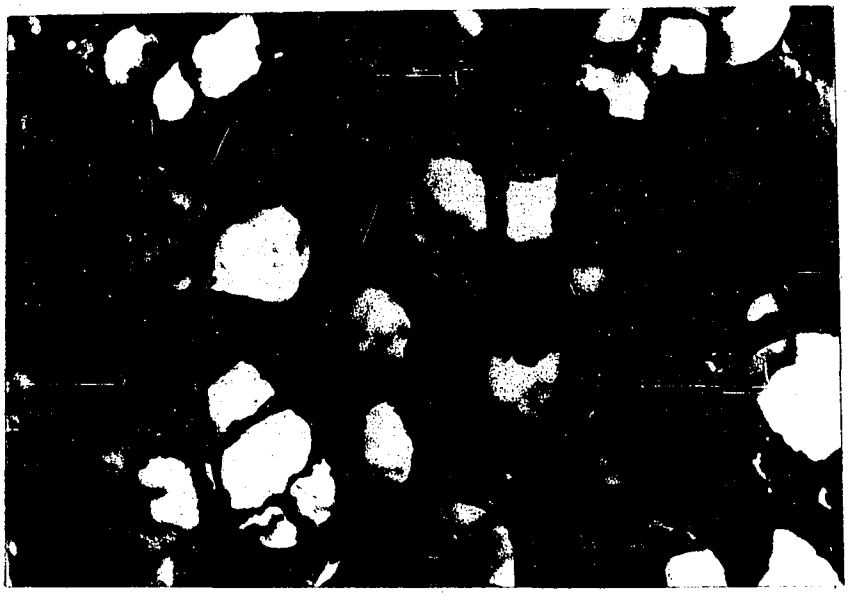


Fig. 46. Photomicrograph of lung section showing normal elastic tissue fibers (elastic tissue stain x 100). Note the dark thick band around alveolar openings.

Fig. 47 A & B. Photomicrograph of histologic sections taken from dogs 9 and 20 showing the amount of elastic tissue has decreased. The elastic tissue fibers are also stretched thinly and disrupted. (x 100).

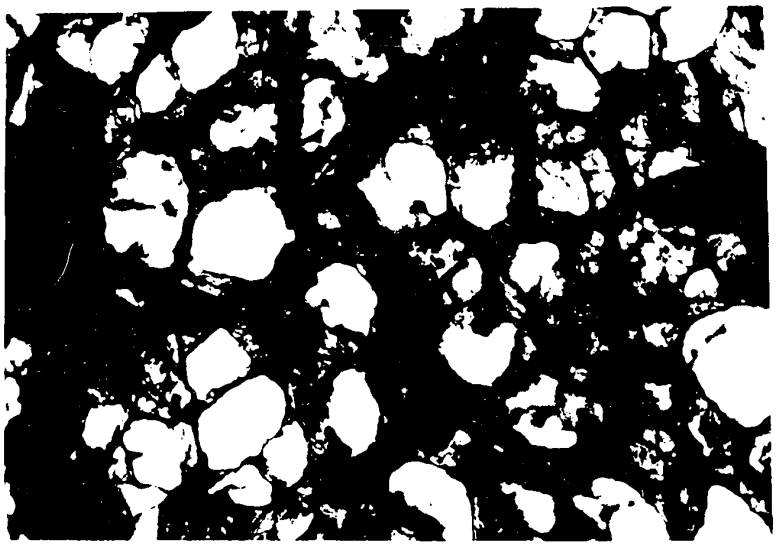


Fig. 46. Photomicrograph of lung section showing normal elastic tissue fibers (elastic tissue stain x 100). Note the dark thick band around alveolar openings.

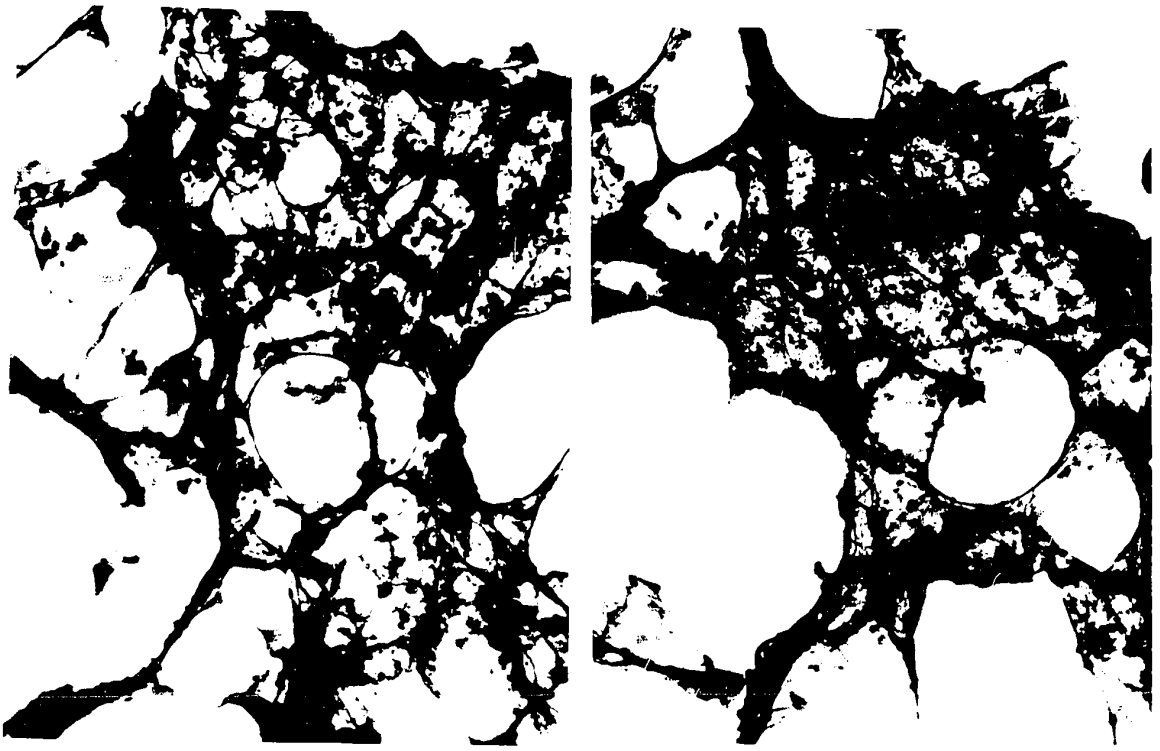


Fig. 47 A & B. Photomicrograph of histologic sections taken from dogs 9 and 20 showing the amount of elastic tissue has decreased. The elastic tissue fibers are also stretched thinly and disrupted. (x 100).

The destructive emphysematous lesion was severe in dog 20 (fig. 40). The sections revealed chronic inflammation of the bronchioles while some of them contained infected mucus plugs (fig. 45).

Elastic tissue stained sections showed disruption and diminution of fibers (fig. 46). These features were observed in all dogs.

Assessment of Emphysema

The results studied are presented in table VII where the values obtained from normal dogs are also given for comparison.

As seen from the table, the assessment of emphysema by point count failed to measure the amount of early panlobular emphysema as seen on gross specimens in most of the dogs.

The mean linear intercepts (the average distance between alveolar walls) in the emphysematous lungs ranged from 0.124 to 0.258 mm.; in the normal lungs they ranged from 0.098 to 0.149. There was some overlapping between the normal and emphysematous lungs. However, the mean values of both groups were definitely different ($P \simeq 0.01$). The mean of the normal group was 0.119 ± 0.017 mm., while that of the emphysematous group was 0.159 ± 0.038 mm. The mean linear intercept was 33.6% increased beyond the normals.

The internal surface area, corrected to an arbitrary lung volume of 2 litres (ISA_2), ranged from 59.0 to 71.2 m^2 in the normal group and from 33.4 to 56.8 m^2 in the emphysematous group. There was no overlapping between groups.

The mean value in the normal group was $65.14 \pm 4.51\ m^2$, and in the emphysematous group it was $46.52 \pm 8.5\ m^2$. The internal surface area was decreased in emphysema by 28.6% of the normal ($P = 0.001$).

DISCUSSION

Lung Volume

Studies of the total pulmonary capacity and its subdivisions in emphysematous patients have been well demonstrated in the past. The persistent finding of a low vital capacity, increased functional residual capacity and residual volume, normal or high total lung capacity are usually presented in the data of lung volume pulmonary function tests of emphysematous patients (10, 27). As mentioned previously, total lung capacity in the present report was arbitrarily measured when the lung was inflated up to a transpulmonary pressure of 30 cm of water. Hence, the vital capacity obtained by this means could not be precisely interpreted or compared with the previously published data. However, the data indicate that the decreased vital capacity in emphysema is due to other causes other than the limitation of the lung expansion because the vital capacity can be further increased by applied pressure.

The measurement of functional residual capacity and residual volume yields results identical with previous investigations (10, 27). Both functional residual capacity and residual volume were increased in all emphysematous dogs.

Christie (22) realized that the increased functional residual capacity was the result of the loss of elastic recoil of the emphysematous lung. This idea is based on the fact that in the normal individual, the

functional residual capacity reflects the balance between the elastic pulling of the lungs and the traction of the chest wall in opposite directions. In emphysema, with the loss of elasticity the lungs must yield to the traction of the chest wall and distend until this force is obliterated: i.e. the volume of the functional residual capacity must increase until the intrapleural pressure fluctuates around that of the atmosphere. The present results confirm this concept by showing the evidence of the loss of recoil pressure, as indicated by the hyper-compliance of the lungs and the intrapleural pressure shifting to a positive value (table V). Histologic examination demonstrated the dilatation of alveolar ducts and alveoli.

Comroe and associates (27) pointed out that increased expiratory obstruction will lead to increased functional residual capacity if expiration is passive and the time for expiration is limited. Frayser (42) produced emphysema in dogs by means of a ball valve partially obstructing the lobar bronchus. He found that the functional residual capacity was increased in dogs with emphysema. Dayman (28) suggested that premature closure of the bronchial tree during expiration may cause air trapping in the emphysematous patient who has no evidence of organic obstruction in the lumen (see page 135). The evidence of air trapping was obvious at necrospy when the excised lung of the dog 20 showed no tendency to collapse completely, and post mortem residual volume was found to have increased about three times the normal value.

Diffusing Capacity and Arterial Blood Gases

As shown in table III, D_{Lco} measured during spontaneous breathing yielded variable results among individual dogs. This is in contrast with D_{Lco} obtained during controlled ventilation (same frequency and tidal volume) where the values were progressively reduced in all dogs. It is apparent that the changes of D_{Lco} in the spontaneous breathing group varied with minute volume. Lorriman (71) reported this effect of increasing minute volume on the elevation of steady state end tidal D_{Lco}. Apthorp and Marshall (4) published that D_{Lco}, measured by end tidal sample, changes with tidal volume. Therefore, it is hard to draw any conclusion from the changes of D_{Lco} in relation to emphysema in the spontaneous breathing group.

Bates (7) showed that the absolute uptake of CO was reduced in emphysematous patients compared with that found in normal subjects with a comparable minute volume and that the fractional removal of CO was reduced. The present report confirms his study.

The decrease of D_{Lco} in progressive reduction of the controlled minute ventilation group might indicate more destructive lesions of emphysema. As observed from histologic sections, the loss of gas exchange area due to destruction of the alveolar walls was comparable with the reduction of D_{Lco}. In such destruction, both the alveolar membranes and pulmonary capillary beds were reduced (129). The measurements of internal

alveolar surface area confirmed that the total area was definitely reduced. The presence of mild bronchitis (dogs 17, 18) or bronchitis with obstruction of small airways (dog 20), theoretically would be additional factors in a lowering of the diffusion because of increased thickness of diffusing pathway and uneven distribution of the gas. But there was no striking difference in the alteration of D_{Lco} among the emphysematous dogs with evidences of bronchitis (dogs 17, 18), or bronchitis with obstruction of airways (dog 20). However, Bates et al (9) found that D_{Lco} end tidal sample was normal in the patient with chronic bronchitis. Shepard and his colleagues (107) found that the reduction of the diffusing capacity in chronic obstructive airway disease was not correlated with the degree of obstruction. Further support of this is shown from the observation that patients with asthma had evidence of increased residual volume and severe impairment of mixing of gases in the lung yet having a normal steady state carbon monoxide diffusing capacity (126).

William and Zohman (125) reported in their studies of emphysematous patients that the lowering of diffusing capacity was not due to diminished blood flow. They cited as evidence for this observation that the average cardiac index in these patients was normal and the diffusing capacity during exercise was reduced for the degree of blood flow obtained. Forster (41) noted that nonuniform distribution of alveolar ventilation/capillary blood flow led to a decrease in steady state D_{Lco}. Since the

presence of abnormality of distribution of ventilation/perfusion ratio in the lungs of patients with emphysema can be inferred from an elevated arterial Pco_2 in the presence of a normal level of minute ventilation (10), hence it can be presumed that there was no such disturbances in all dogs except one which showed small retention of arterial Pco_2 (dog 17).

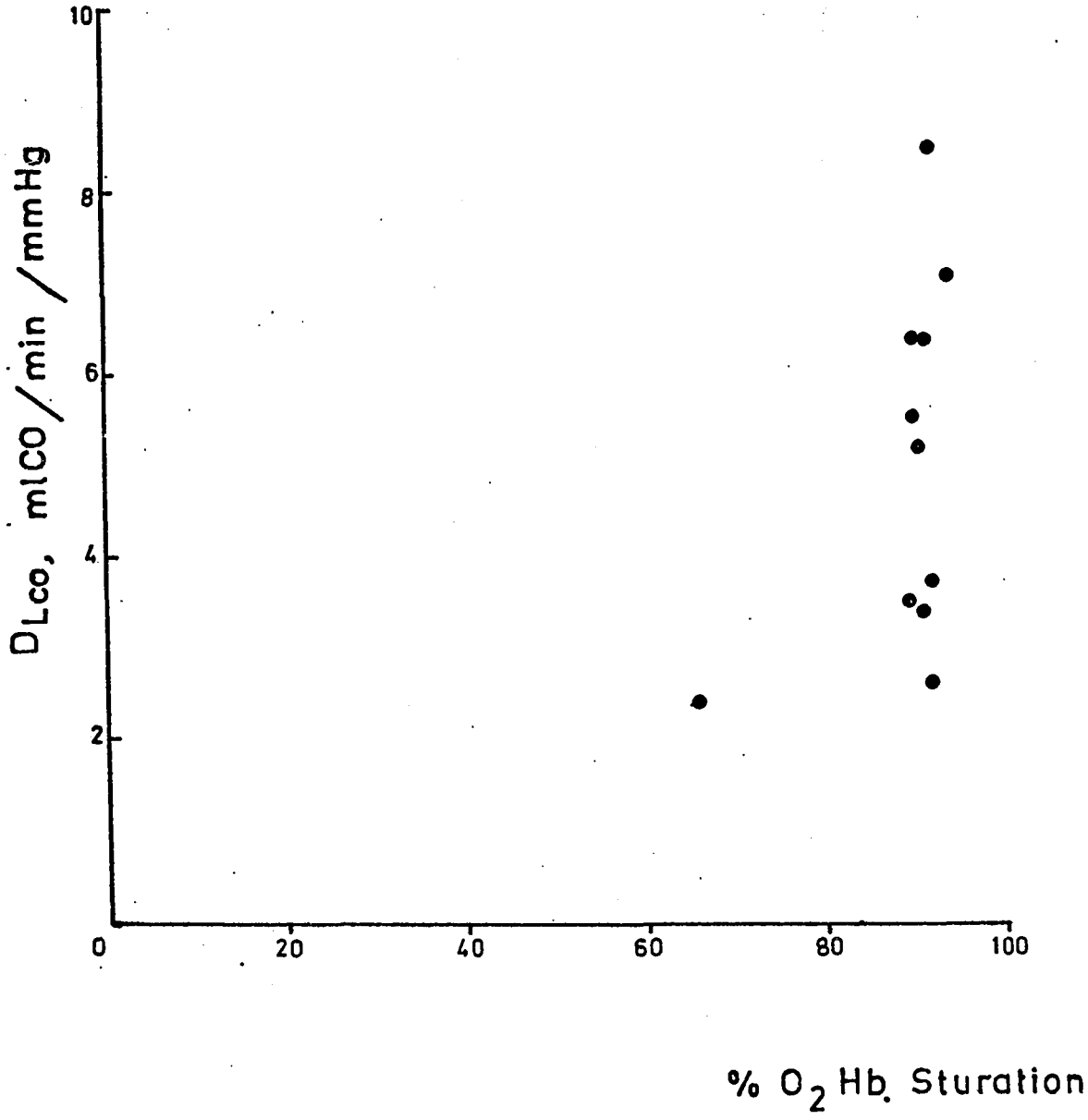
It seems that the limitation of diffusing capacity in emphysema in the present study mostly reflects loss of alveolar-capillary surface.

Patients with chronic pulmonary emphysema are usually found to have anoexemia with elevation of the CO_2 tension and normal blood pH and bicarbonate. Bates (10), noted that in patients with severe pulmonary emphysema the arterial blood might be normal and severe alteration in blood gas tension was commonly found in the patient with coexistent acute exacerbation of infection.

If hypoventilation is not present such as in the measurement under controlled ventilation, a low arterial Po_2 or low arterial oxygen saturation might result from uneven distribution of alveolar gas and blood; from right to left shunt; from a very limited diffusing capacity.

As seen in Table IV, the dog 20 was found to have severe hypoxemia, low Pao_2 and low arterial O_2 saturation, but no CO_2 retention in arterial blood which indicates an adequacy of alveolar ventilation or no disturbance of alveolar gas and capillary blood ratio. Atelectasis was not seen

FIG. 48



at autopsy or in the histologic specimens. Although capillary shunt could not be excluded in the present study, it seems most likely that hypoxemia is due to limited diffusing capacity, since the degree of hypoxemia varied with diffusing capacity.

In contrast, the other dogs showed no relationship between D_{Lco} and hypoxemia (see Fig. 47). This is in agreement with previous reports on emphysematous patients (125). The disorder of the ventilation-perfusion ratio may be presumed from the retention of arterial CO_2 in dog 17. Therefore, the alteration of this ratio would be a factor causing hypoxemia. The retention of arterial CO_2 in the other dogs may be masked by the effect of alveolar hyperventilation as a result of artificial ventilation because in emphysema alveolar ventilation is usually lower than in normal lungs. Alveolar CO_2 will be influenced by this effect. Since CO_2 diffuses 20 times as rapidly as O_2 through the alveolar capillary membrane, hyperventilation therefore leads to a decrease in arterial blood CO_2 which the effect on arterial Po_2 is very small.

However, it may be concluded that the decrease of D_{Lco} was the result of the reduction of the diffusing surface and the disturbance of the ventilation/perfusion ratio. Both also influenced the alteration of arterial CO_2 and O_2. Normal ventilation or hyperventilation was still inadequate to oxygenate the blood in the present study. Any change in the arterial CO_2 disturbed the blood acid-base balance. Plasma bicarbonate was increased to compensate the falling of arterial CO_2 or vice versa. The compensation was complete as indicated by normal pH.

Analysis of group results reveal that the significant alteration of the pulmonary function test was a decrease in D_{Lco}. It was the most sensitive test in early emphysema. Statistical analysis was highly significant at a level less than 0.01, while arterial blood gas shows no significant alteration. This pointed out that arterial blood gases did not reflect early emphysema; i.e. normal arterial blood gases did not exclude pulmonary emphysema.

The Elastic Behaviour of Emphysema

Previous investigations have shown that quasi-static compliance usually increases in a patient with emphysema (21, 74) which is consistent with the present study. Cherniack (21) has reported values as high as three times the normal value. Christie (22) first noted that less transpulmonary pressure is required to maintain a given lung volume in patients with emphysema when measured from tracings of tidal volume and intrapleural pressure. He showed that this evidence resulted from loss of pulmonary elasticity. Similar results were subsequently reported by Dayman (28) and by Stead et al (110). Additional findings by Macklem et al (74) demonstrated that this loss of recoil was more evident when measured

at maximal inflation and was of value in distinguishing emphysema from asthma. This result was confirmed by other workers (57, 120).

Since pulmonary emphysema is characterized by a distortion of lung architecture, pathologists tend to equate lung elastic behaviour with elastic tissue. This idea has received support from Hartroft (51) and Leopold (67). They found that in long standing cases, elastic tissue could not be demonstrated because of a marked destruction of alveolar walls in the affected regions. The present study confirms these reports by showing a moderate reduction of elastic fibers in emphysematous lungs (dogs 15, 16, 17, 18, 19 and 20). Nevertheless, these evidences are in dispute with other reports (61, 92). Kountz and Alexander (61) pointed out that in acute emphysema observed in patients who died from influenzal pneumonia, whooping cough or from bronchial stenosis, elastic tissues were normal. Wright, Kleinerman and Zorn (126) and Pierce et al (93) reported that the amount of elastic and collagen content in emphysematous lungs was no different from that in normal lungs in persons of a similar age, even in severe cases of emphysema. Pierce and others (92) further demonstrated that destruction of the elastic tissue in the lungs with elastase did not produce any significant changes in the elastic properties of lungs filled with

air. However, it may be concluded that the overall elastic behaviour of the lungs is not solely dependent on stress elongation in elastic tissue fibers. In other words, the changes in compliance reflect the recoil pressures of the lung as a whole.

The Flow Resistive Behaviour of Emphysema

It has been shown for a long time that patients with emphysema have increased resistance to breathing. The first important study was by Neergaard and Wirz (122) who, using the intrapleural pressure method, measured the pulmonary resistance in one patient with emphysema. They found that the resistance was increased in emphysema and there was a greater expiratory than inspiratory resistance. These essential findings were also discovered by Dayman (28) in a larger number of emphysematous patients when the same technique was applied. In addition, Dayman observed that the expiratory flow rate was slow and further elevation of the intrathoracic pressure resulted in no increase of expiratory flow rate. Similar results were obtained by a number of investigators with different approaches (45, 56, 74, 79, 96). This is ample evidence of increased airway resistance in emphysema.

In the present study we found that the average values of total pulmonary resistance (expiratory and inspiratory flow resistance) in dogs with emphysema were quite variable (as shown in Table A1 and Fig. 13-20) among individuals or even in the same individual as observed in dogs 17, 18 and 19. However, statistical analysis of the group showed no significant changes. This is in contrast with the resistance obtained by the retrograde catheter method which showed high increased peripheral resistance in all dogs with emphysema (dogs 11-20) and will be discussed later. Since it had been shown that the tissue resistance was small when determined in subjects breathing a small tidal volume (6, 76), it therefore was a negligible factor. It is reasonable to assume that the total airway resistance was not changed in the present study. Our data confirms the observations of Hogg et al (56). They pointed out that one out of nine emphysematous lungs had normal total airway resistance in spite of markedly increased small airway resistance. Park et al (91) reported normal pulmonary resistance in experimental emphysematous hamsters. McFadden and Lyons (72) measured airway resistance in bronchial asthma which is known as an obstructive disease of small airways. They reported that the total airway resistance was brought to normal limits while the lungs of the subjects still showed frequency dependent compliance and uneven ventilation, i.e. increased airflow resistance still existing in the tracheo-bronchial tree. These findings indicate that total airway resistance may not increase with the presence of increased small airway resistance. This is in conflict with other observers who usually found a considerable increase in airway

resistance in emphysema (74). The difference is possibly due to the degree of emphysema present in the lungs of subjects. In the present study, the emphysema produced was so early that the amount of parenchyma involved was not extensive enough to be detected by the measurement made at the mouth. As shown by Macklem and Mead (75), the resistance in peripheral airways of normal dog lungs as well as of human lungs represented only a small percentage of the total pulmonary resistance; 15% of R_L at 10% VC and it was too small to detect over 80% VC. Their calculations indicated that one-half of the peripheral airways could close in a randomly distributed manner throughout the lung, thus halving the peripheral conductance. However, this change would cause only a 10 to 15% increase in total pulmonary resistance. This was confirmed experimentally by Woolcock, Brown and Bates (24). By means of insufflating 2 mm beads they widely obstructed small airways in excised lobes of dog lungs. In spite of a wide obstruction of small airways, there was a minimal effect on total pulmonary resistance.

Central and Peripheral Airway Resistance

The present study shows that airway resistance exists in both large and small airways. In comparison with the previous study on normal dogs (75), we found a large increase in small airway resistance but in

dog 19 the increase was small. By contrast, the big airways showed a small elevation of resistance. Macklem, Fraser and Bates (73) measured bronchial pressure directly at various levels of the bronchial tree from the alveolus to the mouth. They reported that there were two levels at which airway resistance was increased in patients with emphysema. One was at the level of small airways where the resistance was relatively fixed and present during both inspiration and expiration. The other was in the large airways where the resistance was highly variable and present only during expiration. Hogg, Macklem and Thurlbeck (56) carried the studies one step farther. The study was based on a reliable method of measuring pressure in the small airways less than 2 mm in diameter (75). They were able to show that in normal lungs the resistance of the small airways accounted for only a small fraction of the total resistance to airflow. In emphysematous patients this portion of the resistance was increased markedly from 4 to 40 times that of the normal value, while the resistance in the large airways scattered around the normal value. Our data confirms these studies. It is well agreed upon that the small airways are the important portion of the lung and they exert a considerable effect on the increased resistance to airflow in emphysema.

The means by which resistance to airflow is increased in the patient with emphysema is of interest and importance. In the present study, the evidence of obstruction in the airways that would be the cause

of the increased resistance is controversial. The evidence of obstruction is vaguely present in dogs 17, 18, 19 and more obviously in dog 20, where the microscopic sections showed bronchiolitis and bronchioles containing infected mucus plugs in some areas. Bronchiectatic areas also existed in the lungs of dog 20. Post mortem bronchograms showed irregular filling of the small airways. These obstructions were absent in the remaining emphysematous dogs. In this group, the bronchioles were still patent, though mild infection was observed in some areas of the lung.

Laennec (66) was the first who described an obstructive feature of airways in emphysema. He pointed out that the essential lesion was an organic obstruction of the smaller bronchi. This concept is widely supported (3, 56, 77). McLean (77) found that mucus plugging, narrowing and obliteration of the small airways were frequently present in emphysema. Hogg and co-workers studied this in more detail and pointed out that peripheral resistance was increased in airways smaller than 2 mm in diameter because of the organic obstructions.

In other groups of emphysema, intrinsic obstruction of the airways was absent but presented deterioration of pulmonary functions, especially increased resistance. In this case, Neergaard and Wirz (122) theorized the check valve mechanism, but it was investigated in detail by Dayman (28). They pointed out that emphysema might lead to airway obstruction by causing premature closure of small airways. This concept is based on the fact that small airways lack cartilaginous support and

therefore are subject to collapse. But in the normal lung the patency of airways is maintained by a radial traction force from the supporting alveoli. During expiration of the normal respiratory cycle the intrabronchial pressure is less than the alveolar pressure and the pressure difference tends to reduce the caliber of the respiratory tract, thereby increasing pulmonary flow resistance. However, during inspiration the mechanism reverses. This physiological effect on airway resistance was well illustrated by DuBois (33). Direct observation of the respiratory tract from bronchoscopy and bronchography demonstrated tracheal collapse during the rapid expiratory phase of cough effects (30). In emphysema, this phenomena was augmented because the parenchyma had broken down and left the bronchioles unsupported and more vulnerable to collapse during expiration. Fry et al (45) have reported that resistance increased as the lung volume decreased in emphysema. Campbell and his associates (20) obtained similar results. Ting and William (120) showed that in asthma, airway resistance was elevated during both inspiration and expiration, whereas in emphysema the resistance was largely elevated during expiration. The findings indicate excessive dynamic compression of airways during expiration in emphysema. It is reasonable to apply this idea in the present study where we found that all experimental dogs with emphysema showed evidence of: (a) decreased elastic recoil pressure, i.e. loss of tissue tension to keep small airways open; (b) elevated small airway

resistance and evidence of increased resistance with smaller lung volume; (c) increased RV, i.e. more air tapping in the lung without obvious obstruction; and (d) flaccid airways. This evidence is obvious when the percentage change in the diameter of the small airways were compared at an equal higher distending pressure. The change of the airways in emphysema is larger than the controls, but this phenomena reverses when the lung was deflated to a lower lung volume or smaller distending pressures. The change of small airways then became smaller. This evidence indicates that the airway walls were flaccid and tended to close at low lung volumes. There are two possible reasons to explain the instability of small airways at low lung volume. One of the reasons is the loss of the radial traction force just described and the other is related to surface tension force. From the Laplace relationship, the effect of surface tension on the liquid lining of the airway must be greatest when the internal diameter of the airway and distending forces are least. These airways would then become unstable and closed. If peripheral airways are lined with surfactant (which is known to line alveoli and alveolar ducts and possible respiratory bronchioles), their surface tension will be modified and result in a diminished surface force with lung volume. They would therefore tend to be stabilized at low lung volumes. In emphysema, the amount of surfactant could be altered. If it is absent from the peripheral airways, the surface tension would exert its

greatest influence at low lung volume and lead to instability and closure of these airways. The evidence at hand suggests that anatomical changes in emphysema are a factor of increased resistance,particularly during expiratory effort.

We would like to summarize that there are two possible mechanisms causing increased resistance of the small airways in emphysematous lungs in the present study. One is organic obstruction and the other is premature closure of the airways.

Pathological Studies

In the present study, it is apparent that a lesion resembling panlobular emphysema found in humans can be produced in dogs by the intratracheal injection of papain in a dose of 1.0 mg/lb. of body weight. It seems that the extent and severity of emphysema relating to the dosages varies considerably from one dog to another. For example, dog 9, which received 1 mg. of papain per lb. of body weight had more severe emphysema than dog 13 which received 2 mg. of papain per lb. of body weight. Furthermore, in dogs 17 and 18 which received multiple injections of 1 mg./lb./wk. for 4 weeks, the amount of emphysema, as assessed by the internal surface area, did not differ from those which received a single dose of 1 or 2 mg./lb. for a period of 1 or 2 weeks.

The lesion in the present study is that of true destructive panlobular emphysema and is apparently different from the lesion which Gross et al (48, 49) described where the emphysema was initially of the centrilobular type.

The genesis of the lesion is uncertain but since papain is a powerful proteolytic enzyme, the main effect may be on the supporting matrix of the lung, especially the elastic tissue fibers. The small airways which have lost their supporting tissue are vulnerable

to collapse, thereby obstructing these airways. Chronic obstruction of airways has been shown to produce dilatation and destruction of alveoli in dogs (42). The other possibility is the destruction of alveolar walls by the papain enzyme. The alveoli and respiratory bronchioles are vulnerable structures because of their anatomical structure and position. The epithelial lining of respiratory bronchioles and especially that of alveoli is very thin. The alveolar walls are covered merely by extremely thin cytoplasmic extensions of the alveolar epithelial cells while the bronchioles are partly lined by cuboidal epithelium. In contrast, the epithelial lining of the other bronchial air channels is of a relatively thick and ciliated type. Hence, it is possible that the intratracheally injected papain to distal alveoli was rapidly absorbed. Furthermore, since by their anatomical position, they are a collecting structure, the alveoli and respiratory bronchioles were exposed to the highest dose of the papain enzyme which resulted in damage to their walls. The severity of emphysematous lesions in dog 20 was found to be associated with bronchiolitis and obstruction. As this evidence was not found in other dogs, it would be a superimposed factor causing damage rather than the primary cause of emphysema in the present study. McLean (77) has indicated that bronchiolar inflammation, as well as obstruction,

is an important etiological factor in the production of pulmonary emphysema. Gross et al (48, 49) found that emphysematous lesions produced with papain in their experimental animals was not associated with inflammation. Blenkinsopp (13) reported that emphysema rarely followed bronchiolar scarring resulting from acute bronchiolitis or caused by fibrogenic dust foci. Whatever the infection is, an additional factor produced the severe emphysematous lesions as seen in dog 20.

Measurement of Emphysema

It has been shown that the assessment of emphysema by means of point counting yields good correlation with the gross zonal grading or internal surface area measurement in human emphysema (117). In the present study, the emphysematous lesions were trivial. The size of the alveoli in dogs is approximately 2 to 3 times smaller than in humans (estimated by comparing the present data of normal Lm and that of normal human lungs) (115). Hence, the abnormal enlargement of airspaces in dog lungs to a very small degree is difficult to recognize. Prinsloo (95) also emphasized that the method was not sensitive enough to detect the presence of patchy lesions of emphysema which were commonly found in the present study. For these reasons, the point counting

method failed to assess emphysema as seen in histologic sections. However, when the internal surface area (ISA) was expressed at an arbitrary lung volume of 2.0 litres (ISA_2), this value was low in the emphysematous group with no overlap with normal values. The results are comparable with those measured in human emphysematous lungs (34, 36, 54). Dunnill (36) found that all but one patient with panlobular emphysema had a small ISA when compared with the normal value. Duguid et al (34) also found a decreased ISA in emphysema, but they measured it in only one side of the lung. They also found that some of the emphysematous lungs had an ISA value falling within the normal range and this could be abolished by expressing the surface areas to a volume of 3.0 litres. Hicken et al (54) had confirmed these in which both sides of the lungs were measured and the surface areas were calculated to a standard volume of 6.0 litres. However, Thurlbeck (117) with the biggest series of internal surface area measurements found that although the surface area at a standard volume of 5.0 litres could distinguish emphysematous from non-emphysematous lungs, it could not distinguish mild emphysema from non-emphysema. He emphasized that the wide variation of the surface area was presented in non-emphysematous lungs. These studies, however, indicate that the internal surface area expressed to an arbitrary lung volume is useful in distinguishing mild emphysema from the normal condition.

The mean linear intercept values in the present study are substantiated by the previous reports on human emphysema by Thurlbeck (117). He found that Lm measurements of mildly emphysematous lungs fell within the range found for non-emphysematous lungs, but the mean Lm in mild emphysema was different from that in non-emphysema. He also found that Lm corrected to a standard volume did not change the correlation.

Correlation of Degree of Emphysema with Function Studies

As described in previous sections, the sub-divisions of the lung volume D_{Lco}, lung compliance and peripheral resistance were significantly changed in the emphysematous dogs. Comparative studies between these functions and the ISA_2 and Lm were done in the present study. The correlation has been made on both absolute values of these function studies and the percentage changes of the normal values with the ISA_2 or Lm. The coefficient of correlation (r) was calculated and the results are presented in TableVIII.With the exception of the FRC there was no significant correlation between any of the function tests and the degree of emphysema. Thurlbeck, Fraser and Bates (114) found that in 33 cases of varying degrees of emphysema, the sub-divisions of lung volume and D_{Lco} showed a progressive disturbance of function

TABLE VIII

The Correlation of the Function Studies and the Degree of Emphysema

Function Test	Lm		ISA_2	
	r	P	r	P
FRC: absolute value	0.297	0.1	0.725	0.05
% change	0.070	0.1	0.060	0.1-0.05
RV: absolute value	0.428	0.1	0.679	0.1-0.05
% change	0.070	0.1	0.04	0.1-0.05
TLC: absolute value	0.257	0.1	0.68	0.1-0.05
% change	0.020	0.1	0.22	0.1-0.05
D_{Lco}: absolute value	0.736	0.1-0.05	0.517	0.1
% change	0.054	0.1	0.186	0.1
State Compliance: absolute value	0.470	0.1	0.25	0.1
% change	0.028	0.1	0.333	0.1
R_p: absolute value	0.260	0.1	0.02	0.1
% of R_L	0.440	0.1	0.5	0.1

with increasing amount of emphysema. However, there appeared to be no single test to indicate the severity of emphysema. Wyatt, Fischer and Sweet (127) studied pulmonary resistance of post mortem lungs and reported that the resistance increased with the advancement of emphysema. In both of the previous studies the amount of emphysema was estimated from macrosections. In the present study, the degree of emphysema produced was usually mild and the number of cases was small. Nevertheless, the studies reveal that the disturbance in the function studies is due primarily to the structural changes in the emphysema lungs.

CONCLUSION

Minimal to moderate degrees of panlobular emphysema were produced in dogs after intratracheal injection of papain. Function studies showed significant increases in FRC, RV, TLC and decreases in the resting steady state diffusing capacity, the arterial O_2 saturation and Po_2. There was no significant alteration in the pH, PCO_2 and bicarbonate concentration. The compliance increased and the pressure volume curve shifted upward to the left. The pulmonary resistance related to the lung volume was not significantly changed while the resistance in airways less than 2 mm diameter was significantly increased. The mechanisms of the functional disturbances have been discussed. There was no direct correlation between the functional disturbances and the severity of emphysema except between FRC and ISA_2. The studies revealed that the functional changes were the result of the anatomical disturbances in the emphysematous lungs.

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APPENDIX A

TABLE OF AIRWAYS RESISTANCE

TABLE A1 - TOTAL PULMONARY RESISTANCE AT DIFFERENT TRANSPULMONARY PRESSURE

Dog No.	Period (Days)*	Transpulmonary Pressure													
		2 cm.H_2O		4 cm.H_2O		6 cm.H_2O		8 cm.H_2O		10 cm.H_2O		12 cm.H_2O		14 cm.H_2O	
		E	%	E	%	E	%	E	%	E	%	E	%	E	%
9	Control	6.50		5.90		5.50		5.20		5.00		4.50		4.00	
	7	7.70	18.5	6.50	10.2	5.60	0.9	4.60	-11.7	4.50	-10.0	4.05	-10.0	3.60	-10.0
10	Control	4.80		5.90		5.80		5.60		5.10		4.65		-	
	7	5.80	20.8	4.60	-22.0	4.10	-29.3	4.40	-21.4	4.25	-16.7	4.10	11.8	-	-
11	Control	4.80		4.10		3.85		3.40		3.40		3.40		3.40	
	7	6.30	31.3	5.15	25.6	5.00	29.9	4.05	19.1	3.70	8.8	3.90	14.7	4.20	23.5
13	Control	5.20		3.80		3.60		3.80		3.75		3.90		4.30	
	14	5.20	0.0	5.50	44.7	5.10	41.7	5.05	3.29	5.00	33.3	4.60	18.0	4.90	14.0
16	Control	5.80		5.60		5.10		4.40		3.80		3.60		4.80	
	14	5.00	-14.7	4.50	-18.9	4.40	-13.7	4.55	3.4	4.70	23.7	4.80	33.3	4.50	-6.3
17	Control	4.40		3.90		3.50		3.10		3.00		2.8		2.70	
	14	3.20	18.0	3.50	-20.5	2.80	-20.0	2.5	-19.35	2.30	-23.3	2.30	-19.6	2.30	-14.8
	28	6.10	38.6	6.00	53.9	5.20	48.6	4.4	41.9	4.20	40.0	4.10	44.6	4.10	50.0
18	Control	3.90		3.40		3.60		3.20		2.80		2.90		3.00	
	14	4.90	25.6	4.10	20.6	3.70	2.8	4.05	26.6	3.70	32.1	3.40	17.2	3.50	16.7
	28	4.20	7.7	3.40	0.0	3.25	-9.7	3.30	3.1	3.00	7.1	2.60	-10.3	2.70	-10.0
19	Control	5.00		4.60		4.10		4.20		4.30		3.6		3.50	
	14	5.60	12.0	4.90	6.5	4.65	13.4	5.00	19.1	4.40	2.3	4.10	12.5	3.70	4.3
	28	5.20	4.0	4.60	0.0	3.30	4.9	4.70	11.9	4.50	4.7	4.40	22.2	4.00	11.4

* days after papain injection; E = Experimental measurement; % = Percentage change from the control value

TABLE A2

Airways Resistance, Measured on Excised Lung
by the Retrograde Catheter Technique

Dog No.	Catheter site in an airway (dia)	Period* (days)	Transpulmonary Pressure											
			2 cm H_2O				4 cm H_2O				6 cm H_2O			
			R_L	R_C	R_P	R_P (% R_L)	R_L	R_C	R_P	R_P (% R_L)	R_L	R_C	R_P	R_P (% R_L)
11	1 mm	7	3.89	1.32	2.57	66.0	1.36	0.48	0.88	64.7	1.82	0.57	1.25	68.7
13	1.6 mm	14	11.25	2.60	8.65	76.9	7.30	1.80	5.50	75.3	6.15	1.45	4.70	76.4
15	1.2 mm	14	11.85	3.65	8.20	69.2	5.70	2.30	3.40	59.7	6.55	2.65	3.90	59.5
16	1.8 mm	14	7.10	2.10	5.00	70.5	3.55	1.05	2.50	70.4	2.90	0.95	1.95	67.2
17	1.6 mm	28	-	-	-	-	6.99	1.14	5.85	83.4	7.50	0.63	6.85	91.4
18	1.0 mm	28	8.30	2.10	6.20	74.7	4.35	1.40	2.95	67.8	4.50	1.70	2.80	62.2
19	1.0 mm	28	-	-	-	-	4.00	2.70	1.30	32.5	3.40	2.80	0.60	17.7
20	1.0 mm	28	7.55	1.73	5.82	77.0	6.35	1.37	4.98	78.4	4.75	1.30	3.55	74.8

R_L = total airway resistance; R_C = central airway resistance (resistance in an airway bigger than 2 mm internal diameter); R_P = peripheral airway resistance (resistance in an airway smaller than 2 mm internal diameter).* Period of study after papain.

TABLE A2
(Continued)

Dog No.	8 cm H_2O				10 cm H_2O				12 cm H_2O				14 cm H_2O			
	R_L	R_C	R_P	R_P (% R_L)	R_L	R_C	R_P	R_P (% R_P)	R_L	R_C	R_P	R_P (% R_P)	R_L	R_C	R_P	R_P (% R_P)
11	1.84	0.58	1.26	68.5	1.67	0.57	1.10	65.9	1.32	0.54	0.78	59.1	-	-	-	-
13	3.80	1.00	2.80	73.7	3.45	1.00	2.45	71.0	3.10	1.00	2.10	67.7	-	-	-	-
15	6.10	2.70	3.40	55.7	6.60	2.80	3.80	57.6	8.40	3.30	5.10	60.7	10.10	3.80	6.30	62.4
16	2.45	1.00	1.45	59.2	2.80	1.50	1.30	46.4	3.60	1.80	1.80	50.0	4.20	2.00	2.20	52.4
17	7.37	1.20	6.17	83.5	6.83	1.38	5.45	79.8	6.57	1.25	5.32	81.0	6.21	1.11	5.20	82.1
18	3.45	1.15	2.30	66.7	6.05	2.75	3.30	54.6	-	-	-	-	-	-	-	-
19	3.90	3.10	0.80	20.5	4.30	3.30	1.00	23.3	5.20	3.65	1.55	29.8	5.20	3.70	1.50	28.9
20	4.10	1.10	3.00	73.2	5.53	1.28	4.25	76.7	7.10	1.55	5.55	78.2	6.29	1.50	4.79	76.2

TABLE A3 STATISTIC ANALYSIS OF R_L, R_C R_p

	Transpulmonary Pressure													
	2 cm H_2O		4 cm H_2O		6 cm H_2O		8 cm H_2O		10 cm H_2O		12 cm H_2O		14 cm H_2O	
	Mean±SE	P	Mean±SE	P	Mean±SE	P	Mean±SE	P	Mean±SE	P	Mean±SE	P	Mean±SE	P
R_L:C	5.05±0.27	0.1-0.05	4.64±0.33	0.5-0.3	4.38±0.31	0.7-0.5	4.11±0.30	0.5-0.3	3.89±0.28	0.3-0.2	3.67±0.22	0.2-0.1	3.67±0.26	0.3-0.2
E	5.68±0.35		5.03±0.32		4.61±0.25		4.38±0.17		4.23±0.21		4.06±0.22		3.98±0.25	
R_C:C	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	2.25±0.30		1.57±0.34		1.51±0.28		1.48±0.30		1.02±0.33		1.87±0.41		2.42±0.50	
R_p:C	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6.07±0.85		3.42±0.62		3.20±0.67		2.65±0.56		2.83±0.54		3.17±0.72		4.00±0.82	

Res.* = resistance
R_L = pulmonary flow resistance
R_C = central airway resistance
R_p = peripheral airway resistance
C = control
E = experiment

APPENDIX B

TABLE OF DIAMETER OF TRACHEO BRONCHIAL TREE

TABLE B1

Diameter of Tracheo Bronchial Tree, Normal Dog 1

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	18.60	18.74	19.18	19.18	19.20
1	16.43	16.61	16.69	17.02	17.08
2	13.32	15.08	15.96	16.08	16.13
3	9.86	11.54	13.52	15.23	15.52
4	7.01	8.57	9.74	11.28	12.24
5	6.72	6.86	7.59	8.69	8.97
6	5.78	5.83	5.95	6.11	6.94
7	5.36	5.45	5.72	5.90	6.26
8	4.52	4.55	4.62	4.79	5.08
9	4.03	4.07	4.10	4.15	4.19
10	2.01	2.33	2.47	2.68	2.87
11	1.81	1.89	1.92	2.15	2.20
12	1.77	1.83	1.85	2.27	2.29
13	1.40	1.47	1.51	2.02	2.11
14	1.32	1.32	1.33	1.58	1.66
15	0.93	0.96	1.00	1.08	1.13
16	0.52	0.54	0.54	0.84	0.91
Left Lung					
1	13.54	13.72	13.90	14.06	14.08
2	8.98	10.18	10.75	11.76	11.76
3	5.97	6.80	7.45	8.78	9.16
4	4.69	5.49	6.00	7.87	8.38
5	3.55	5.20	5.40	6.19	6.24
6	3.76	3.79	4.01	5.08	5.47
7	4.13	4.84	4.84	4.96	4.99
8	3.19	3.22	3.24	3.28	3.31
9	2.89	2.96	2.99	3.01	3.08
10	1.85	1.85	1.86	2.10	2.18
11	1.10	1.20	1.22	1.46	1.55
12	0.85	0.88	0.89	0.99	1.03
13	0.82	0.84	0.87	0.95	1.02

*0 = Trachea
1 = Main Bronchus

TABLE B2

Diameter of Tracheo Bronchial Tree, Normal Dog 2

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	14.30	14.50	15.29	16.54	16.95
1	13.69	15.18	15.91	16.02	16.55
2	9.03	11.38	12.64	13.25	13.28
3	9.76	11.92	13.51	13.73	13.73
4	8.06	10.77	11.60	11.71	12.03
5	6.38	8.14	8.48	8.51	8.55
6	5.03	6.95	7.14	7.29	7.39
7	4.27	5.36	5.49	5.64	5.70
8	4.09	5.20	5.29	5.45	5.46
9	4.75	4.94	4.98	5.11	5.25
10	3.83	3.99	4.14	4.35	4.39
11	2.98	3.03	3.10	3.19	3.27
12	2.08	2.40	2.42	2.45	2.47
13	2.18	2.21	2.25	2.36	2.39
14	1.52	1.53	1.58	1.59	1.61
Left Lung					
1	9.23	11.24	11.61	12.23	12.23
2	8.39	9.50	9.85	9.89	9.85
3	5.95	7.75	8.23	8.40	8.47
4	4.91	5.85	6.18	6.25	6.25
5	4.35	5.07	5.22	5.33	5.38
6	4.18	4.99	5.20	5.28	5.31
7	3.96	4.55	4.73	4.84	4.87
8	3.30	3.61	3.82	4.03	4.04
9	2.97	3.16	3.34	3.37	3.38
10	2.43	2.77	2.95	3.02	3.08
11	2.23	2.28	2.42	2.51	2.50
12	2.09	2.26	2.40	2.45	2.45
13	1.38	1.43	1.58	1.60	1.61
14	0.83	1.16	1.26	1.30	1.30

*0 = Trachea
1 = Main Bronchus

TABLE B3

Diameter of Tracheo Bronchial Tree, Normal Dog 3

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	16.47	16.91	17.76	18.24	18.40
1	15.73	17.13	17.89	18.52	18.55
2	11.50	13.99	15.58	16.37	17.53
3	11.89	13.40	14.95	15.97	16.26
4	9.81	11.18	12.43	13.42	13.42
5	8.07	8.61	9.10	9.77	9.83
6	5.28	6.36	7.13	7.62	7.89
7	4.77	5.41	6.03	6.49	6.53
8	5.24	5.69	5.98	6.35	6.46
9	4.34	4.88	5.27	5.39	5.76
10	3.22	3.79	4.15	4.33	4.42
11	2.44	3.05	3.36	3.58	3.59
12	1.92	2.03	2.36	2.45	2.53
13	1.29	1.71	2.00	2.15	2.43
14	1.24	1.51	1.74	1.84	1.84
Left Lung					
1	11.66	12.58	13.60	14.18	14.46
2	10.99	12.09	12.94	13.27	13.55
3	8.18	9.38	10.30	11.01	11.05
4	6.48	7.33	8.38	8.65	8.85
5	5.48	6.35	7.07	7.86	7.95
6	3.46	4.73	5.69	6.49	7.33
7	3.34	4.34	5.11	5.66	5.80
8	3.21	3.98	4.60	5.02	5.22
9	3.01	3.64	3.90	4.03	4.50
10	2.99	3.59	3.92	4.36	4.43
11	2.28	2.92	3.41	3.76	3.93
12	2.13	2.86	2.98	3.26	3.37
13	1.86	2.44	2.70	2.96	3.01
14	1.84	2.51	2.70	2.89	2.98

*0 = Trachea
1 = Main Bronchus

TABLE B4

Diameter of Tracheo Bronchial Tree, Normal Dog 4

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	16.56	16.54	17.17	18.66	19.03
1	14.35	15.12	16.28	16.81	17.04
2	12.93	14.80	16.12	17.99	18.31
3	11.83	14.30	15.66	16.95	17.11
4	8.71	10.54	12.60	13.95	14.01
5	5.40	6.12	7.68	10.18	10.18
6	3.88	5.62	6.34	8.86	8.96
7	3.56	4.14	5.43	8.06	8.20
8	5.19	5.21	5.62	6.64	6.77
9	3.02	3.06	3.28	4.76	4.76
10	1.64	1.78	1.85	3.70	3.81
11	0.75	1.03	1.39	2.93	2.98
12	0.46	0.59	0.81	1.58	1.63
Left Lung					
1	11.80	12.72	13.35	14.72	15.06
2	11.26	12.14	12.98	13.39	13.42
3	6.94	7.94	9.64	11.68	11.68
4	5.02	5.83	7.63	9.39	9.52
5	4.28	4.39	5.63	7.44	7.67
6	5.41	5.23	5.71	6.96	6.98
7	2.76	3.09	3.68	5.17	5.23
8	1.89	2.22	2.72	4.13	4.22
9	1.55	1.71	2.17	3.50	3.65
10	1.47	1.61	2.09	3.37	3.52
11	0.85	0.94	1.26	2.23	2.35

*0 = Trachea
1 = Main Bronchus

TABLE B5

Diameter of Tracheo Bronchial Tree, Normal Dog 5

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	19.73	19.73	20.83	21.66	22.30
1	19.83	21.03	21.34	21.98	22.23
2	15.79	13.02	18.94	19.85	20.00
3	14.10	16.03	16.46	17.78	17.78
4	10.32	13.42	14.99	15.08	15.08
5	9.43	9.81	10.32	10.45	10.52
6	6.74	7.66	8.56	8.93	9.03
7	5.73	6.40	6.58	7.03	7.18
8	5.12	5.29	5.63	5.92	6.04
9	4.67	4.78	4.81	4.84	4.87
10	4.00	4.34	4.57	4.61	4.64
11	3.14	4.03	4.20	4.21	4.21
12	2.75	2.96	3.17	3.18	3.20
13	1.98	2.88	3.09	3.15	3.15
Left Lung					
1	16.17	17.29	18.18	19.04	19.04
2	11.08	12.34	12.81	12.82	12.91
3	8.71	9.80	10.40	10.57	10.64
4	7.35	7.86	8.06	8.68	8.88
5	6.07	6.09	6.30	6.40	6.49
6	5.98	6.04	6.19	6.41	6.61
7	5.04	5.14	5.38	5.43	5.54
8	4.59	4.86	5.23	5.54	5.74
9	3.26	3.53	3.95	4.20	4.21
10	3.03	3.08	3.16	3.16	3.19
11	2.03	2.23	2.56	3.12	2.81

*0 = Trachea
1 = Main Bronchus

TABLE B6

Diameter of Tracheo Bronchial Tree, Normal Dog 6

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	18.34	19.17	19.65	20.60	21.15
1	18.07	19.74	20.46	20.80	21.34
2	14.03	16.32	16.95	17.44	17.86
3	13.79	14.36	15.32	16.36	16.85
4	10.05	12.04	12.86	14.30	14.20
5	6.99	9.71	10.74	11.59	11.91
6	5.86	7.91	8.48	9.41	9.93
7	4.82	6.53	6.90	7.73	8.17
8	3.72	4.50	4.93	5.72	5.95
9	5.05	4.75	4.82	5.21	5.36
10	3.31	3.66	3.68	3.77	3.90
11	2.61	2.93	2.97	3.18	3.25
12	1.43	1.73	1.86	2.19	2.20
13	1.25	1.60	1.81	2.11	2.11
Left Lung					
1	13.90	14.98	15.40	15.55	15.70
2	10.20	12.20	13.19	13.61	13.36
3	8.61	10.10	11.24	11.95	11.96
4	6.45	7.94	8.87	9.55	9.72
5	5.58	6.56	6.87	7.19	7.29
6	5.93	5.90	6.49	6.94	7.19
7	5.18	5.00	6.17	6.56	6.70
8	2.60	3.49	3.98	4.48	4.79
9	2.32	2.73	3.04	3.43	3.51
10	2.01	2.66	2.94	3.22	3.29
11	1.92	2.65	2.97	3.06	3.05
12	1.44	2.26	2.40	2.60	2.63
13	1.72	1.98	2.12	2.39	2.50
14	1.36	1.75	2.06	2.30	2.39

*0 = Trachea
1 = Main Bronchus

TABLE B7

Diameter of Tracheo-Bronchial Tree, Papain Dog 16

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	-	18.59	19.08	19.30	19.48
1	-	18.59	20.27	20.77	20.89
2	-	18.26	18.64	18.96	18.96
3	-	15.78	16.56	17.15	17.21
4	-	12.82	13.25	13.39	13.70
5	-	9.07	9.40	9.68	9.87
6	-	6.17	6.39	6.46	6.48
7	-	4.55	4.86	5.11	5.21
8	-	4.25	4.43	4.48	4.48
9	-	3.51	3.75	3.81	4.90
10	-	2.42	2.68	2.78	2.79
11	-	2.36	2.62	2.76	2.83
12	-	1.94	2.05	2.30	2.37
13	-	1.65	1.84	1.92	2.07
14	-	1.33	1.55	1.78	1.93
15	-	1.30	1.55	1.79	1.82
16	-	1.00	1.27	1.46	1.63
Left Lung					
1	-	15.87	16.06	16.23	16.16
2	-	14.11	14.42	14.64	14.69
3	-	12.77	13.32	13.42	13.67
4	-	10.30	10.48	10.66	10.77
5	-	7.30	7.48	7.65	7.73
6	-	6.53	6.58	6.75	6.81
7	-	6.06	6.06	6.20	6.26
8	-	5.36	5.41	5.55	5.60
9	-	3.37	3.64	3192	3.96
10	-	3.20	3.39	3.54	3.67
11	-	2.85	3.00	3.15	3.40
12	-	2.34	2.67	2.73	3.00

*0 = Trachea
1 = Main Bronchus

TABLE B8

Diameter of Tracheo-Bronchial Tree, Papain Dog 17

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	15.27	18.98	20.12	20.95	21.40
1	17.85	20.38	21.22	21.28	21.31
2	12.17	15.74	16.65	17.98	18.15
3	11.78	15.36	15.80	16.18	16.66
4	7.17	10.25	10.26	12.59	12.69
5	4.17	5.52	5.57	7.02	7.20
6	4.81	6.00	6.20	7.25	7.33
7	3.25	3.30	3.51	4.10	4.23
8	2.07	2.52	2.46	3.27	3.42
9	1.80	2.22	2.13	3.12	3.32
10	1.02	1.16	1.07	2.00	2.07
11	1.05	1.04	1.03	1.15	1.20
12	1.00	1.01	1.01	1.03	1.19
13	0.90	0.89	0.90	1.04	1.00
14	1.64	1.65	1.73	1.73	1.71
15	1.32	1.32	1.71	1.74	1.84
16	0.99	1.00	0.99	0.99	1.06
17	0.85	0.88	0.87	0.88	0.88
Left Lung					
1	12.00	14.92	15.97	17.10	17.16
2	10.43	12.60	13.09	13.79	13.76
3	6.61	9.08	9.15	11.41	11.64
4	2.77	4.27	4.28	6.22	6.47
5	2.75	3.81	3.93	5.62	5.78
6	1.17	2.00	2.04	3.09	3.25

*0 = Trachea
1 = Main Bronchus

TABLE B9

Diameter of Tracheo-Bronchial Tree, Papain Dog 18

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	19.39	20.03	20.11	20.60	20.90
1	16.08	18.02	19.48	19.58	19.66
2	15.33	19.28	20.81	21.00	21.47
3	13.58	17.71	18.85	19.63	19.98
4	12.71	16.25	16.39	16.90	17.79
5	8.58	11.95	13.29	13.48	13.49
6	7.97	11.39	12.44	12.78	12.89
7	5.95	8.18	8.94	9.09	8.97
8	6.02	6.50	7.33	7.53	7.55
9	4.11	5.34	7.25	7.50	7.53
10	3.57	3.90	5.25	5.40	5.52
11	3.26	3.38	4.54	4.74	4.91
12	2.73	2.91	3.79	4.01	4.24

*0 = Trachea
1 = Main Bronchus

TABLE B10

Diameter of Tracheo-Bronchial Tree, Papain Dog 19

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	16.63	17.14	17.26	17.43	17.67
1	15.48	16.68	17.19	17.44	17.61
2	9.40	12.12	14.12	14.28	14.53
3	8.64	10.02	11.28	13.61	13.98
4	5.73	8.61	10.35	11.08	11.60
5	4.87	7.83	8.48	10.38	10.68
6	4.92	6.31	7.00	7.72	8.03
7	6.51	6.66	6.82	7.11	7.54
8	5.34	5.63	5.82	5.92	5.95
9	4.82	4.84	4.88	4.93	4.94
10	3.69	3.58	3.68	3.85	4.02
11	1.81	2.15	2.70	3.06	3.25
12	1.29	1.69	2.00	2.44	2.63
13	1.22	1.42	1.86	1.98	1.98
Left Lung					
1	11.26	12.22	13.03	13.42	14.00
2	9.24	11.96	12.98	13.26	13.50
3	5.39	7.65	9.01	9.80	10.08
4	4.23	5.49	6.37	7.40	7.80
5	4.65	4.66	5.55	6.80	7.16
6	3.65	3.01	4.03	4.47	4.73
7	2.33	2.66	2.85	3.27	3.54
8	1.63	2.05	2.53	3.17	3.36
9	1.43	1.86	2.39	3.03	3.13

*0 = Trachea
1 = Main Bronchus

TABLE B11

Diameter of Tracheo-Bronchial Tree, Papain Dog 20

Broncheal* Generation	Distending Pressure, cm H_2O				
	0	5	10	20	30
Right Lung	mm.	mm.	mm.	mm.	mm.
0	13.98	14.46	14.66	15.15	15.20
1	15.67	17.71	18.08	18.96	19.25
2	11.11	12.67	13.45	15.50	15.57
3	9.94	11.37	11.76	13.32	13.36
4	10.08	10.84	11.50	12.40	12.77
5	9.64	10.22	10.32	10.54	10.57
6	8.46	8.63	8.80	8.99	9.03
7	5.78	6.02	6.08	6.33	6.40
8	5.47	5.76	5.78	5.90	6.00
9	4.98	5.20	5.20	5.30	5.35
10	2.13	2.24	2.24	2.26	2.39
11	1.42	1.72	1.82	2.35	2.47
12	1.39	1.44	1.49	1.64	1.66
13	1.00	1.12	1.17	1.40	1.47
Left Lung					
1	8.59	9.40	9.44	9.68	9.91
2	8.95	9.59	9.79	10.60	11.01
3	7.34	8.30	8.51	9.06	9.24
4	5.24	5.77	6.11	6.74	6.85
5	3.92	4.07	4.28	4.91	5.23
6	3.08	3.62	4.06	4.50	4.98
7	3.07	3.21	3.39	3.86	4.70
8	2.40	2.59	2.75	2.78	2.95
9	1.82	1.90	2.18	2.51	2.51
10	1.43	1.44	1.46	1.59	1.77
11	1.06	1.22	1.29	1.45	1.47
12	0.58	1.02	1.09	1.13	1.21

*0 = Trachea
1 = Main Bronchus