COMPENSATORY LUNG GROWTH FOLLOWING PNEUMONECTOMY IN PUPPIES

A Thesis
presented to
the University of Manitoba

In partial fulfilment
of the requirements for
the Degree of Master of Science

by

Mary Ellen Arnup

1983

COMPENSATORY LUNG GROWTH FOLLOWING PNEUMONECTOMY IN PUPPIES

BY

MARY ELLEN ARNUP

A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Table of Contents

Acknowledgements

I would like to take this opportunity to thank all of the many people who made this project possible. I am especially grateful to: Dr. N.R. Anthonisen for his valuable comments and assistance with the experiments and in preparing this manuscript. Dr. H.W. Greville for his assistance with the experiments and analysis and particularly for his constant encouragement and enthusiasm. Dr. L. Oppenheimer who kindly performed the surgical procedures. Dr. S.N. Mink who provided much advice on the flow data. Mary Cheung for her statistical expertise. And finally, Ross Boyle for assisting with the electronics.

ABSTRACT

We performed left pneumonectomy (P) in 9 puppies at 10 weeks of age; 8 littermates underwent a sham operation and functioned as controls (C). All were studied at 25 weeks of age. In group P all lobes of the right lung increased in weight relative to group C, the increase being greatest in the cardiac lobe. There was no difference in lung weight/body weight, TLC/body weight or lung elastic recoil between the two groups. There was also no difference in the compliance of the chest wall. However, maximum expiratory flow rates at 50% and 25% vital capacity were reduced by 60% and 56% respectively in group P. Surprisingly, in pneumonectomized animals, there was no drop in $\dot{V}max_{50}$, the percent increase of $\dot{V}max_{50}$ on helium over that on air. Using ^{133}Xe, the distributions of ventilation and perfusion were compared between right and left hemithorax. The distribution of boluses inhaled slowly from FRC, determined largely by compliance, was reduced in the left hemithorax. In these dogs perfusion was also reduced on the left. Rapidly inhaled boluses of ^{133}Xe are distributed according to regional conductances and the distribution of such boluses was decreased in the left hemithorax of all P dogs, averaging 67% of that on the right. We conclude that following pneumonectomy, airway growth is substantially less than parenchymal growth and probably results in increased frictional losses upstream from the flow limiting segment during maximum expiration. This is at least partly due

to increased resistance in regions which have undergone the most growth and are located in the left hemithorax.

List of Tables

List of Figures

I. INTRODUCTION

Early in fetal life the airways are formed with the mature alveoli developing after birth, increasing in number and then in size, until growth of the chest wall is complete at adulthood. There has been much interest in the postnatal development of the lung and how this growth may be affected by trauma such as pneumonectomy. Several factors are known to influence postnatal lung growth. Hypoxia in early life results in an increase in the number of alveoli while hypoxia during later life causes hypertrophy of existing structures in the lung (1). Many hormones alter normal lung growth. A deficiency of growth hormone suppresses normal lung development while an excess induces hypertrophy (1). Cortisone and thyroid hormone are deemed important to lung growth (1) and there is evidence to support the theory that cortisone may enhance the maturation of alveolar type II cells during development. Exercise or increased oxygen consumption seems to cause an increase in the diffusing capacity of the lung which may reflect a change in lung structure (2). Chronic stresses placed on the lung by deformation of the chest wall also influence lung structure. Children with kyphoscoliosis causing areas of the lung to be compressed show a lack of alveolar development in the affected regions (3). Protein malnutrition in young animals also interferes with alveolar proliferation (3). In light of these changes it became of interest to consider the ability of the remaining lung to undergo compensatory growth following pneumonectomy.

Except for one or two human studies examining changes in lung function after pneumonectomy, most of the work to date has been biochemical or morphometric. There has been much controversy over the nature of the adaptive response to pneumonectomy. Biochemical assays of the adapted lung show that there is an increase in DNA

synthesis (4,5,6). The RNA/DNA ratio remains unchanged, indicating a proliferation of lung cells (6). This DNA synthesis seems to affect all cells in the remaining lung in rats. It peaks in endothelial cells by 1.3 days, in interstitial cells by 5.2 days and in pleural cells by 7.8 days (4). DNA synthesis more than tripled in alveolar walls throughout this 8 day period. Cowan and Crystal (7) found that the total lung collagen increased following surgery. Most of the cell proliferation could be accounted for by alveolar type II cells, some of which differentiate into type I cells as in the period of normal postnatal growth (4,6).

In all species studied there has been growth of the remaining lung until its weight and volume is the same as both lungs of control animals (2,4-13). However there is much debate over how this compensation is achieved. One school of thought argues that the increase is due to the enlargement of existing lung structures. Buhain and Brody found that the compensatory lung growth in rats undergoing left pneumonectomy consisted of equal enlargement of alveoli and alveolar ducts (5), without an increase in the total number of either. Burri and Sehovic reported similar results when they resected the upper and middle lobes of the right lung in rats at an early age (2). Sery and coworkers found that there was a redistribution of the volume between lung compartments in rabbits who had several months to recover from right pneumonectomy (12). Although the volume of the remaining lung more than doubled to equal the lung volume of control animals, there was a decrease in the portion of alveolar air with a large increase in the portion of alveolar duct air. There was a decrease in the number of alveoli and alveolar ducts per unit volume indicating hypertrophy of existing units. Davies et al. found evidence for the enlargement of

pre-existing structures in pneumonectomized beagle dogs (14). An increase in the size of the distal air spaces as well as the total volume of alveolar ducts and mean alveolar volume was found. The surface density of alveolar epithelium was reduced and the absolute alveolar surface area calculated from these values did not compensate for the tissue lost.

On the other hand, there is much evidence to support alveolar multiplication as a part of lung compensatory growth. Young rats that are allowed to recover from a left pneumonectomy seem to experience alveolar proliferation (9,11). Nattie et al. found that this multiplication was limited to the surface alveoli (11). Others agree, having shown that there is a decrease in surface area of internal alveoli (12). Alveolar multiplication has been observed after pneumonectomy in young rabbits (8,10). Thurlbeck et al. found that the total number of alveoli in one lung of pneumonectomized puppies equalled that of both lungs of control dogs (13). The number of alveoli per unit volume was the same in the right lung and both lungs of control dogs and was no different from the values obtained for the remaining lung in the treated dogs.

Discrepanicies between studies might be due to the timing of the surgery. As pointed out by many authors, there is a definite time schedule of lung development (3,15,16). Meyrick and Reid found that there was a rapid burst of alveolar multiplication 3-8 days postnatally in rats (17). Holmes and Thurlbeck, in a careful study of normal rat lung development showed that alveolar multiplication was prominent again from 4-10 weeks of age (9). There was no further multiplication until 14 weeks when there was further development of the alveolar septae. The adaptive response to pneumonectomy is dependent on the age of the animal. Holmes and

Thurlbeck found that there was no change in the number of alveoli in the remaining lung when adult rats underwent pneumonectomy, but there was alveolar enlargement as indicated by an increased alveolar surface area per unit volume (9). Others found that the compensatory growth in older animals followed a similar pattern as that found in young operated animals, but the growth occurred at a much slower rate (11). This compensation in older animals may be due mainly to enlargement of alveolar ducts or existing alveoli, rather than due to alveolar multiplication (5,14).

The adaptive response appears to be greatest in the areas of lung experiencing the most pleural stress. With the sudden removal of one lung there is an alteration of the pressure within the thorax and a shift of the mediastinum. It is possible that stretch is a major stimulating factor for the adaptive lung growth. Langston et al.(10) found a greater response in the lower lobe of pneumonectomized rabbits, while Thurlbeck et al.(13) reported similar results from canine studies. Davies et al.(14), also using a canine model, concluded that the adaptive response was greatest in the intermediate lobe of the remaining lung. Support for the theory of stretch as a stimulant for growth comes from studies in which liquid paraffin embedding wax was poured into the hemithorax following pneumonectomy (4,7). This procedure, which prevents stretch of the contralateral lung, eliminated the increase in cell number, collagen synthesis, and DNA synthesis in all alveoli, interstitial and endothelial cells. This suggests that control of lung growth or cell differentiaton via gene expression may in part be controlled by available space in the thorax.

Reports of the development of the pulmonary circulation suggest that it too is very susceptible to injury at certain times during

maturation (16,17). Reid (16) states that the arteries which accompany preacinar airways are present sixteen weeks after conception in humans. Blood vessels in the alveolar region appear when the alveoli develop postnatally. Growth of these vessels keep pace with alveolar development but muscularization of the vessels lags behind. Muscularization is linked to artery size and decreases as intra-acinar arteries become more peripheral. Remodelling of the pulmonary circulation occurs into adolescence with the wall thickness and muscle developing in relation to the size and position of the artery. Therefore any treatment which alters the growth and development of alveoli must alter the accompanying vasculature.

The removal of one lung places a great stress on the contralateral pulmonary circulation immediately post surgery. A left pneumonectomy increases right pulmonary blood flow by 75% (18). The size of the lumen and thickness of a vessel wall are affected by the degree of distension of the lumen. Removal of the left lung results in alteration of the size of the lumen and the wall of the right pulmonary artery and its branches as the entire cardiac output is now forced through fewer pulmonary vessels. Numerous studies have examined the effect of such procedures on the pulmonary circulation.

Rudolph et al.(19) studied the effects of left pneumonectomy or left pulmonary artery occlusion on the pulmonary circulation of adult dogs and puppies of 4-8 weeks of age. Following treatment, all dogs showed an immediate sharp rise in mean pulmonary artery pressure (PAP) although this was more prominent in the young pups. Massion and Schilling (20) obtained similar results in adult and young (one week old) pups undergoing upper lobe resection. It is suggested that the different response between young and old animals

might be related to differences in histological features of the vessels. In the immature animal, the wall of the pulmonary artery is thicker and less compliant and therefore is not able to compensate for the excess volume as well as the vessels of an adult dog. Arteriograms suggest that there is dilatation of the pulmonary artery but this is much more prominent in adult dogs (20). Further measurement of PAP shows that it continues to rise slowly in both adult dogs and pups over the subsequent 18 months (19). Kato et al.(18) studied 13 beagle dogs 3 weeks after a left pneumonectomy, when they were 7-11 weeks old. 4 of these were followed progressively until 19 weeks post surgery. They also studied 7 unoperated control animals. Kato and his coworkers found no immediate rise in resting PAP in the pneumonectomized dogs, nor did they find any increase in PAP over time. The only difference between this work and that of Rudolph et al.(19) and Massion and Schilling (20) is the use of beagle dogs as opposed to mongrels and the timing of the studies. Kato et al.(18) did find a rise in PAP following left pneumonectomy in 11-17 week old minipigs. In the one adult and one pup studied by Rudolph et al.(19) there was no change in cardiac output (C.O.) over an 18 month period. Kato et al.(18) found no alteration in C.O. in any of the 7 pneumonectomized puppies they studied.

In humans, pulmonary hypertension causes increased muscularization of all pulmonary arteries, although the muscle cells do not extend into smaller arteries (16). This seems to be the case for hypertension arising from pneumonectomy in animals. In all dogs young or old, receiving either left pulmonary artery occlusion or left pneumonectomy, there was alteration of the medium and small arteries of the right lung (12). The intermediate vessels appeared

to be more dilated and tortuous, with thickening of the intima and medial layers and with occasional fibrous plaques. Davies et al.(14) found similar but slightly different results. Their study involved dogs that underwent pneumonectomy as either adults or as 6-10 week old puppies, and were studied 5 years after surgery. They found the weight of the right ventricle compared to the combined weight of the left ventricle and septum to be greater in young operated animals. However the percent medial thickness (%MT) of preacinar arteries was similar for young operated and control animals while being significantly higher in dogs that had undergone pneumonectomy as adults. The %MT of intra-acinar arteries was also consistently higher in the adult group. The adults had more muscular or partially muscular small arteries than either young operated or control animals.

It seems that pneumonectomy at any age may result in pulmonary hypertension, but how the circulatory system adapts to this change depends on the age of the animal both at the time of surgery and at the time of study. The expansion of the remaining lung may elongate and narrow existing vessels with a resulting decrease in perfusion to that lung (20,21). The resulting hypertension will probably cause a concomitant medial hypertrophy and dilatation of the right pulmonary artery and its major branches.

With these numerous examples of pulmonary compensation following pneumonectomy at an early age, it became of interest to explore the effects of such trauma on the mechanical function of the lung. We therefore designed the present study to examine several aspects of lung function following compensatory growth. We wished to determine the effect of such surgery on the static recoil of the lung and chest wall. We also hoped to address the question of

whether there was equal compensatory growth of both the parenchyma and the airways by studying the flow-volume relationship of the adapted lung. The use of the radioactive xenon technique was used to provide an insight into the distribution of ventilation and perfusion of these lungs and to indicate any alterations in lung regions which had undergone the greatest degree of growth.

II. EXPERIMENTAL DESIGN

A. Methods

B. Equipment

C. Calibrations

A. Methods

Three litters of mongrel puppies were studied. At ten weeks of age three males and six females underwent left pneumonectomy. The remaining littermates, matched for weight and sex, underwent a sham operation consisting of a left thoracotomy without penetration of the pleural space. The animals were then returned to the vivarium for fifteen weeks. At 25 weeks of age, studies of static and dynamic lung mechanics and regional lung function were carried out. This protocol is the same as that of Thurlbeck et al.(13) and we are therefore able to extend their morphometric findings to our study.

On the day of study, each animal was anesthetized with pentobarbital (30 mg/kg) and a femoral venous catheter inserted to maintain anesthesia as required. A tracheostomy was performed and a rigid endotracheal tube (25 cm length, 1.6 cm ID) was inserted. A sideport on the tube was connected to one side of a differential pressure transducer (Validyne, range $\pm$ 40 cm H_2O) which allowed us to measure airway opening pressure (P_{AO}). A thin-walled balloon was placed in the esophagus 2 cm cephalad from the point of maximum cardiac artifact. This is approximately equal to pleural pressure (P_{pl}). Balloon volume was 1.0 ml, and each balloon demonstrated zero pressure over a volume range of 0.5-1.0 ml. The balloon was connected via a catheter (50 cm length, 1.6 mm ID) to the other side of the differential transducer (P_{pl}), so that the output of the transducer was transpulmonary pressure ($P_L=P_{AO}-P_{pl}$) as described by Petit and Milic-Emili (22). A Swan-Ganz catheter (110 cm length, 0.77 m^2 CSA) was positioned in the right ventricle to allow injection of radioactive xenon.

The dog was then placed in the prone position in a constant-pressure plethysmograph (Emerson, N.J.), the volume of which was sensed by a Krogh spirometer. Between measurements the dog was connected to a Harvard (Mass.) respirator via plastic tubing.

Using the principles of Boyle's Law, we were able to measure lung volumes as developed by DuBois, Comroe and co-workers (23-25). Boyle's law states that for a constant mass of gas the pressure and volume is a constant so long as temperature is constant. During inspiratory efforts against a closed airway the dog decompressed the lung gas. The pressure change associated with these efforts was measured at the airway opening and the volume change was reflected by change in the plethysmograph volume. Thus:

$$\text{FRC or } V_{TG} = -\Delta V/\Delta P \quad (P_I + \Delta P)$$

Since ΔP is very small compared to $(P_I + \Delta P)$ then as it approaches zero $(P_I + \Delta P)$ approaches P_I and the equation becomes:

$$V_{TG} = -P_I \times \Delta V/\Delta P = P_{ATM} \times \Delta V/\Delta P$$

where P_{ATM} is atmospheric pressure, ΔV and ΔP are the changes in volume and pressure respectively, which are measured during inspiratory efforts against a closed airway. Knowledge of ΔV, ΔP and barometric pressure allows calculation of FRC. FRC was measured three times in this way. Each measurement was preceded by an inflation to a transpulmonary pressure of 30 cm H_2O to assure a constant volume history.

With knowledge of FRC, other subdivisions of lung volume could be calculated, given maximum inflations and deflations of the lung. These were accomplished by inflating and deflating the animal from FRC with a plastic syringe while observing the volume change of the

plethysmograph. The volume at maximal deflation, RV, was defined as the volume remaining in the lungs when airway pressure was -10 cm H_2O. The volume at maximal inflation, TLC, was defined as the volume in the lungs where the transpulmonary pressure was 30 cm H_2O. Each inflation and deflation was repeated three times.

We studied the elastic properties of the lung and chest wall by measuring their static pressure-volume characteristics during deflation. Following an inflation to TLC and deflation to FRC, the dog was again inflated to a P_L of 30 cm H_2O and then slowly deflated stepwise. Plethysmograph and therefore respiratory system volume were recorded, as were airway opening pressures, and transpulmonary pressure. The former represented pressure across the entire respiratory system; the latter the pressure across the lung. The difference ($P_{AO} - P_L$) represented the pressure across the chest wall. Therefore at a series of volumes we measured the static recoil pressures across the lungs, chest wall and the two together.

Regional lung function was measured using the ^{133}Xenon technique of Anthonisen et al.(26). The animal was placed supine over an array of scintillation counters fitted with slit collimators. Six counters, 5 cm apart, ranged from apex to base of each hemithorax with no overlap between the fields. Each hemithorax was therefore divided into lung regions and regions from the two sides, located the same distance from the lung apex, could be compared. The arrangement of the counters was such that gravitational differences in lung function were not observed. The distributions of regional compliance, regional resistance and regional perfusion were assessed and side to side comparisons made.

Compliance (C) is the term relating static or semi-static change in volume (ΔV) to change in elastic recoil pressure (ΔP_{el}):

$$C = \Delta V / \Delta P_{el}$$

Among regions, the distribution of gas which is inhaled very slowly (semi-statically) is related to regional pressure changes and regional compliances. If regional pressure changes are the same, then the regional distribution of ventilation (ΔV) is directly proportional to regional compliance. We measured the regional distribution of boluses of ^{133}Xe during very slow inflation. The animal was inflated to TLC and deflated to FRC. During apnea at FRC a bolus of ^{133}Xe (approximately 2 mc in 3 cc of air) was injected into the endotracheal tube. The animal was then slowly (0.1-0.2 l/s) inflated to TLC with a large plastic syringe, the airway occluded, and count rates from each lung region recorded. This procedure was carried out at least twice in each animal.

Regional resistance (R) relates regional flow ($\dot{V}$) to resistive pressure drop (Pr):

$$R = Pr / \dot{V}$$

At the onset of an inflation induced by positive airway pressure, regional airway pressure drops are equal, since all alveoli are at atmospheric pressure and the positive airway opening pressure is common to all regions. When regional pressure drops are equal, the regional distribution of gas inhaled at the onset of a very fast (high flow) inspiration is inversely proportional to regional resistance (27). We assessed regional resistance using an approach similar to that used for regional compliance; instead, however, of distributing the ^{133}Xe boluses with a slow inflation, a very high speed (5.0 l/s) inflation was used. At least two such measurements were made in each animal.

Regional distribution of perfusion was assessed by the intravenous injections of boluses of ^{133}Xe dissolved in saline. Such boluses are distributed in the lung according to blood flow distribution. When ^{133}Xe arrives at the alveoli, its solubility is such that 85-95% of the injected bolus evolves from the blood to alveolar gas, where it remains long enough to be counted. After an inflation to TLC, the animals were deflated to FRC and a bolus of ^{133}Xe (2 mc in 3 cc of saline) was injected intravenously during apnea. Apnea was maintained until the ^{133}Xe evolved into the alveolar gas as revealed by monitoring the regional counters. The animal was then slowly inflated to TLC and the airway occluded while regional count rates were recorded. This maneuver was carried out at least twice in each animal.

Thus we measured regional count rates at TLC after slow and fast inhalations of xenon boluses and after intravenous injection of boluses. Regional count rates reflect the amount of isotope in a region, given the geometry and radiation-attenuating properties of the region. The amount of isotope in a region is a function of regional volume and regional concentration. The most appropriate index of bolus distribution is regional isotope concentration related to that in the lung as a whole. To derive this index, a rebreathing procedure was carried out. The animals inhaled a bolus of ^{133}Xe and, by inflating and deflating them with a plastic syringe, were made to rebreathe the isotope until all regional count rates were constant as a function of time, indicating that all lung regions and the syringe, had the same ^{133}Xe concentration. The animals were then inflated to TLC and regional count rates recorded.

Regional count rates after administration of a bolus (Ub) are related to regional concentration (Fb):

$$Ub = Fb \lambda V$$

where V is regional volume and λ is a factor accounting for regional geometry, attenuation, etc.

Similarly, after equilibration regional count rates (Ue) relate to regional concentrations (Fe):

$$Ue = Fe \lambda V$$

When the same region, at a constant lung volume is considered:

$$Ub/Ue = Fb/Fe$$

Since Fe is constant from region to region, variations in Ub/Ue are due to variations in Fb, and Ub/Ue is an index of Fb in relation to a fixed standard. However this index is not normalized to account for differing amounts of isotope in the lung as a whole during the two procedures - that is, equilibration and bolus administration.

The sum of regional counts after bolus administration (ΣUb) as a fraction of the sum of counts after equilibration (ΣUe) reflects the amount of isotope in the lung after the two procedures, since all measurements are made at constant lung volume so that factors relating to regional volume and attenuation are constant. Therefore:

$$\frac{Ub/Ue}{\Sigma Ub/\Sigma Ue} \times 100 = \dot{V}_I \text{ or } \dot{Q}_I$$

where $\dot{V}_I$ or $\dot{Q}_I$ are ventilation and perfusion indices, respectively, which reflect the distribution of inhaled or injected boluses. If regional ventilation or perfusion were even, all regional indices would be 100. $\dot{V}_I$ were calculated to assess regional compliance and resistance and $\dot{Q}_I$ to reflect regional perfusion.

Each dog was then returned to the plethysmograph, secured in the supine position, and mechanically ventilated with room air. Transpulmonary pressure (P_L) was again measured as noted above.

Gas flow in and out of the plethysmograph and its integral, volume, were plotted against each other on the oscilloscope. The dog was inflated to TLC with either compressed air or a gas mixture of 20% O_2 and 80% He and then exposed to a very negative (-80 to -200 cm H_2O) reservoir pressure, resulting in a forced deflation during which flow was recorded as a function of volume. The maneuvers were repeated in triplicate with each of the two inspired gas mixtures. In each case resevoir pressure was so negative that further changes in this pressure did not alter the MEFV. Integrated plethysmograph volume was plotted against flow on the oscilloscope so that maximum expiratory flow was displayed as a function of volume, the maximum expiratory flow volume curve (MEFV). $\dot{V}max_{25}$ and $\dot{V}max_{50}$, the flow at 25% and 50% VC respectively, were obtained by taking the mean of the flow at those volumes for each condition. The helium response was calculated so that:

$$\Delta \dot{V}_{max} = \frac{\dot{V}_{HeO_2} - \dot{V}_{air}}{\dot{V}_{air}} \times 100$$

where $\dot{V}_{HeO_2}$ and $\dot{V}_{air}$ are the flows noted while breathing the helium-oxygen mixture or room air gas respectively. The helium response was calculated for 50% and 25% VC.

The dog was then heparinized and exsanguinated through the femoral artery. The lungs were carefully removed, weighed and their minimal volumes measured by saline displacement, as dictated by Archemedes Law. The trapped gas volume, with the trachea exposed to atmospheric pressure, was calculated assuming a lung tissue specific gravity of 1.06 so:

trapped gas = volume displaced - (weight of lungs x 1.06)

The lungs, attached to a water manometer and freely suspended,

were slowly inflated several times using a syringe to an airway pressure of 25 cm H_2O and allowed to deflate. They were then inflated to 30 cm H_2O pressure and a static deflation pressure-volume curve obtained. This was repeated until the results were consistent. The trachea was then dissected away and the lungs weighed again. The major bronchi were then cut away, separating the lung into its component lobes and the weight of each lobe was noted.

All comparisons between control and pneumonectomy of the weights and volumes were analyzed using a two-tailed Student's t-test with the appropriate degrees of freedom (28). The analysis of $\dot{V}max_{25}$ and $\dot{V}max_{50}$ involved a paired t-test (29) comparing pneumonectomy and control littermates, matched on the basis of weight and sex. This pairing reduced extraneous influences on the variable being measured. That is, pairing reduces the effect of dog-to-dog variability. A significance level of 5% (α =0.05) was used. This means that the chance of making a Type II error is less than 5%.

The pressure-volume and flow-volume curves were analyzed with a repeated measures analysis of variance (30). Again a significance level of 0.05 was used in examination of the F statistic for differences between curves.

A multiple linear correlation analysis was applied to determine any relationship between $\dot{V}max_{50}$ and the regional resistance measurements obtained from the xenon studies (28).

B. Equipment

In order to rapidly measure the volume of gas in the lungs we have used a pressure-volume plethysmograph (Fig.1). The plethysmograph is a closed box with an opening into a water-filled Krogh spirometer (Emerson, Mass.). Any alteration in the volume of air inside the plethysmograph will cause the air to be expanded or compressed, with resulting displacement of the Krogh spirometer. With an animal inside the plethysmograph, a change in the volume of the respiratory system is reflected by a proportional change in the volume of the box, as detected by the spirometer. The Krogh spirometer consists of a lightweight metal bell which floats in a trough of water on the plethysmograph, resting on two pivots. An opening in the top of the plethysmograph allows communication between the box and the bell. Two springs attached to the bell over the pivots allow the bell to rise at the front when the volume of air inside the bell increases. The change in volume is detected by a linear variable differential transformer (43). The solid metal core which alters the output voltage of the transformer is attached to the spirometer bell by a fine string. As the bell rises and falls, the position of the core is altered and a change in volume detected.

A Validyne DP15 pressure transducer (Validyne, CA.) is used to measure compression or expansion of air and a flow meter set in the box wall is a resistance element which will monitor the airflow. The transducer is arranged to sense the difference between the box interior and ambient pressure (P_{box}). At any instant, the pressure difference is proportional to the rate of airflow through the meter;

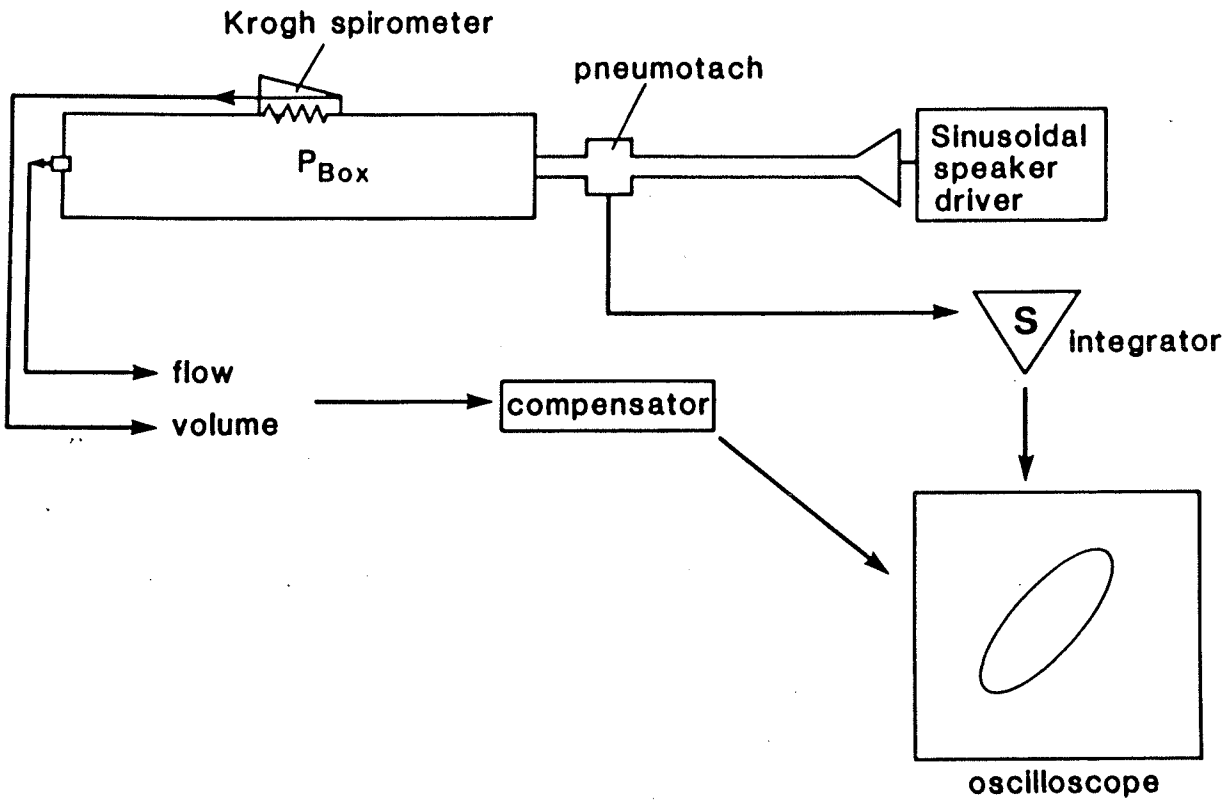

Figure 1: Schematic representation of the plethysmograph apparatus as used during dynamic calibration.

it also measures gas compression or expansion in the box. Integration of the pressure (flow) signal provides a continous record of the volume which has passed through the flow meter, and adding P_{box} to the integral provides the correction necessary for the fraction of the dog's volume change which is accounted for by compression or expansion in the box (29).

In order to calculate the lung volume we utilize Boyle's Law. At end-inspiration and end-expiration the gas in the lungs is at atmospheric pressure, P_{ATM}. If the airway is closed at the end of a normal expiration, the gas within the chest is trapped at that lung volume (FRC). When the dog pants against the occluded airway, the changes in pressure measured at the mouth (which equal alveolar pressure) are reflected by changes in the pressure within the box. We are able to calculate the original volume of gas in the lungs by examining the changes in pressure and volume during the panting maneuver. Thus:

$$V_{TG} = P_{ATM} \times \Delta V / \Delta P$$

where V_{TG} is thoracic gas volume, P_{ATM} is atmospheric pressure, ΔV and ΔP are the change in volume and pressure respectively.

Other lung volumes such as RV and TLC were measured by recording the plethysmograph volume while the animal was inflated or deflated as described above.

The apparatus for monitoring radioactive xenon consisted of 6 slit collimator counters positioned vertically under each side of the dog, spaced 5 cm apart ranging from the apex to base of the thorax. The collimation was arranged so that there was little overlap from the point source, ie. the area seen by one counter. The output of the counters was amplified and processed by digital

rate meters, the output of which were plotted on a 12 channel oscillograph (Hewlett-Packard, Mass.). We were unable to analyze all of the data due to inadequate count rates. In most dogs the apical count rates were extremely low and in some dogs the most basal count rates were also of no use.

For measurement of flow-volume curves we utilized the flow meter in the wall of the plethysmograph. The output of the pneumotachograph connected directly to an oscilloscope provided a measure of airflow, while integration of this signal gave a volume signal with a more sensitive frequency response than that of the Krogh spirometer. This volume signal was corrected for P_{box} and connected to the oscilloscope.

C. CALIBRATIONS

I) The following procedures were performed before each litter was studied.

1) Volume correction for Pbox.

Integration of the pressure (flow) signal provides a continuous record of the volume which has passed through the flow meter. However this signal differs from the true volume signal by a fraction of the animal's volume change which is accounted for by gas compression or expansion in the box. This may be corrected by adding the appropriate value of P_{box} to the integrated flow signal.

As seen in Figure 1, volume in the box was subjected to oscillatory change by a sinusoidal speaker driver. Box flow was sensed with a pneumotachograph and this signal integrated. The resulting volume output was plotted on an oscilloscope (Tektronix, Ore). The volume signal from the Krogh spirometer was passed to a compensator and the output plotted on the other axis of the oscilloscope. If the integrated signal for box volume did not adequately compensate for changes in P_{box}, it was out of phase with the oscillator volume, and looping was observed on the oscilloscope. A signal proportional to P_{box} was applied to the box volume signal and when the P_{box} gain was appropriately adjusted, looping was eliminated and the two volume signals were in phase. Adjustments were made so that the two signals were in phase up to an oscillatory frequency of 7 Hz.

2) Flow correction for Pbox

In this case the output of the pneumotachograph of the sine wave generator passed directly to the oscilloscope and was plotted against the flow signal from the box. A signal proportional to the time derivative of P_{box} was applied to the box flow signal and adjusted until box flow and speaker flow were in phase, again determined by the absence of looping on the oscilloscope. This adjustment was made so that the two flow signals were in phase up to a frequency of 7 Hz.

II) These calibrations preceded each study:

1) Electrical Balancing

With no input, the electrical balance of the preamplifiers, the transducers, the Hewlett-Packard recorder and the oscilloscope were checked over a wide range of gain settings.

2) Validyne Pressure Transducer

a) With no pressure input, the zero was set at a convenient place on the oscilloscope and recorder. Using a water manometer, 20 cm H_2O positive pressure was added to the positive side of the transducer. The oscilloscope was adjusted so that 20 divisions represented 20 cm H_2O. This pressure was noted on the recorder and was usually equal to 19 divisions on the paper and was not adjustable.

b) The linearity of the transducer was checked over a wide range of 0-40 cm H_2O.

c) The procedure was repeated for the negative side of the transducer using an equivilent negative pressure. Again the linearity was checked.

d) Before each run the zero was checked and adjusted as necessary. Occasional checks of the transducer during the course of an experiment showed that it was very stable.

3) Plethysmograph Volume

a) The position of the core of the Krogh spirometer was checked to ensure that the spirometer bell was operating in the central linear region of its range.

b) With the bell in the lower range, the plethysmograph was sealed and zero set at a convenient place on the oscilloscope and recorder. A volume of 1 litre was added to the box and the calibration adjusted so that 1 litre was represented by 20 divisions on the recorder or on the x-axis of the scope.

Any leaks in the system could be detected at this time by a change in the volume signal.

c) A precise calibration of the volume of the plethysmograph was done just prior to measurement of thoracic gas volumes. With the dog inside the sealed box, 10 cc of air was injected via a syringe and the output signal measured on a sensitive gain setting of the recorder. This was represented by a deflection of 10 divisions. This calibration was repeated several times and an average value used for calcultions of the results.

4) Plethysmograph Flow

Zero was set at a convenient place on the oscilloscope and on the recorder. Using a rotameter, a series of constant, known flows were imposed on the plethysmograph and the output from the plethysmograph adjusted. A flow of 2 l/s was represented by a 10 division deflection on the oscilloscope and by a 20 division change

on the recorder.

5) Scintillation Counters

An alternating current of 115 volts was passed through the rate meters and these were adjusted to give 3600 counts per minute. Zeros were set on the oscillograph when no radioactivity was present. A sample of ^{133}Xe was passed over each counter and the output on the oscillograph adjusted so that each gave the same proportion of deflection on the paper.

III. RESULTS

The mean data reflecting lung size of pneumonectomy (P) and control (C) groups are reported in Table I. The mean body weights of each group were not different, with C averaging 18.1 ± 2.5 kg and P 17.1 ± 1.39 kg. Total lung weights, normalized for body weight, were also not different. Both lungs of group C had a mean weight of 9.0 ± 0.48 gm/kg body weight while in group P the single remaning lung averaged 8.5 ± 0.61 gm/kg body weight. The trapped gas volume of the excised lung prior to inflation was not different between the two groups (Table I), with C=111.0 ± 8.8 cc and P=121.1 ± 36.6 cc. Total lung capacity (TLC) in vivo, normalized for body weight, is reported in Table II. The mean control TLC was 130.7 ± 12.8 cc/kg and was not different from the TLC of 120.0 ± 11.5 cc/kg reported for P. There was no difference in TLC measured in vivo and that measured in vitro. Other lung volumes were normalized in terms of TLC. There was a trend towards a slightly greater FRC/TLC in P dogs (38.6 ± 4.9) compared to C dogs (35.9 ± 4.7). The mean RV/TLC was significantly higher ($p < 0.01$) in P dogs than in C animals (C=10.9 ± 1.5 vs P=15.6 ± 2.7).

Lobar weights were assessed in terms of percent lung weight (Table I). The weights of all remaining lobes in pneumonectomized animals were significantly greater ($p < 0.05$) than the corresponding lobes in control dogs. The right upper lobe (RUL) weight increased 58% above the weight of control RUL (C=16.1 ± 0.34 gm vs P=25.4 ± 0.42 gm) while the right middle lobe (RML) was increased 49% in P dogs (C=10.4 ± 1.10 gm vs P=15.5 ± 0.76 gm). The right lower lobe (RLL) weight in experimental animals was 41% greater than the RLL weight of

TABLE I

	CONTROL		PNEUMONEX		
	$\bar{X}$	S.D.	$\bar{X}$	S.D.	
Body Weight (KG)	18.1	±2.5	17.1	±1.39	N.S.
Lung Weight/B.Wt.	9.0	±0.48	8.5	±0.61	N.S.
	(Both Lungs)				*P < 0.05
RUL (% Lung Wt.)	16.1	±0.34	25.4	±0.42	58% ↑ *
RML	10.4	±1.10	15.5	±0.76	49% ↑ *
CL	9.0	±0.22	23.1	±0.58	156% ↑ *
RLL	24.6	±0.30	34.6	±1.09	41% ↑ *
Trapped Gas (cc)	111.0	±8.8	121.1	±36.6	NS

TABLE II

LUNG VOLUMES

	Control (N=7)		Pneumo (N=8)		
TLC/kg	130.7	+12.8	120.0	+11.5	N.S.
FRC/TLC	35.85	+ 4.67	38.63	+ 4.93	N.S.
RV/TLC	10.86	+ 1.46	15.63	+ 2.70	P < .01

control animals (C=24.6 $\pm$ 0.3 gm vs P=34.6 $\pm$ 1.1 gm). The greatest increase was seen in the cardiac lobe (CL) of P dogs, which increased 156% over the weight in control dogs (C=9.0 $\pm$ 0.2 gm vs P=23.1 $\pm$ 0.6 gm). This vast increase in the size of the cardiac lobe may be clearly seen in Figure 2. This photo is indicative of the position of the intact lung in pneumonectomized puppies. There is a slight shift of the mediastinum to the left with the cardiac lobe extending posteriorly into the left hemithorax, and filling most of its lower regions. No fluid was present in the left hemithorax.

Figure 3 shows static pressure-volume curves as measured in the intact animals. The top shows the mean curve of the entire respiratory system (P_{AO}) and indicates that there was no significant difference between the two groups, beyond that which is associated with the larger RV of the pneumonectomized animals. This was tested with a repeated measures analysis of variance (30). The lower panel is the static pressure-volume curve of the intact lung (P_L). Again, there was no difference between the curves. Figure 4 is the mean pressure-volume curve of the chest wall (P_{CW}) for each condition, obtained by mathematical subtraction of ($P_{AO} - P_L$) at each pressure. There was no significant difference between the two curves. A comparison of the excised pressure-volume curves of the lung is made in Figure 5. Again, there was no significant difference between pneumonectomized and control animals. There was also no difference between the intact and excised curves of the lung for either group.

Mean flow-volume curves recorded during inhalations of room

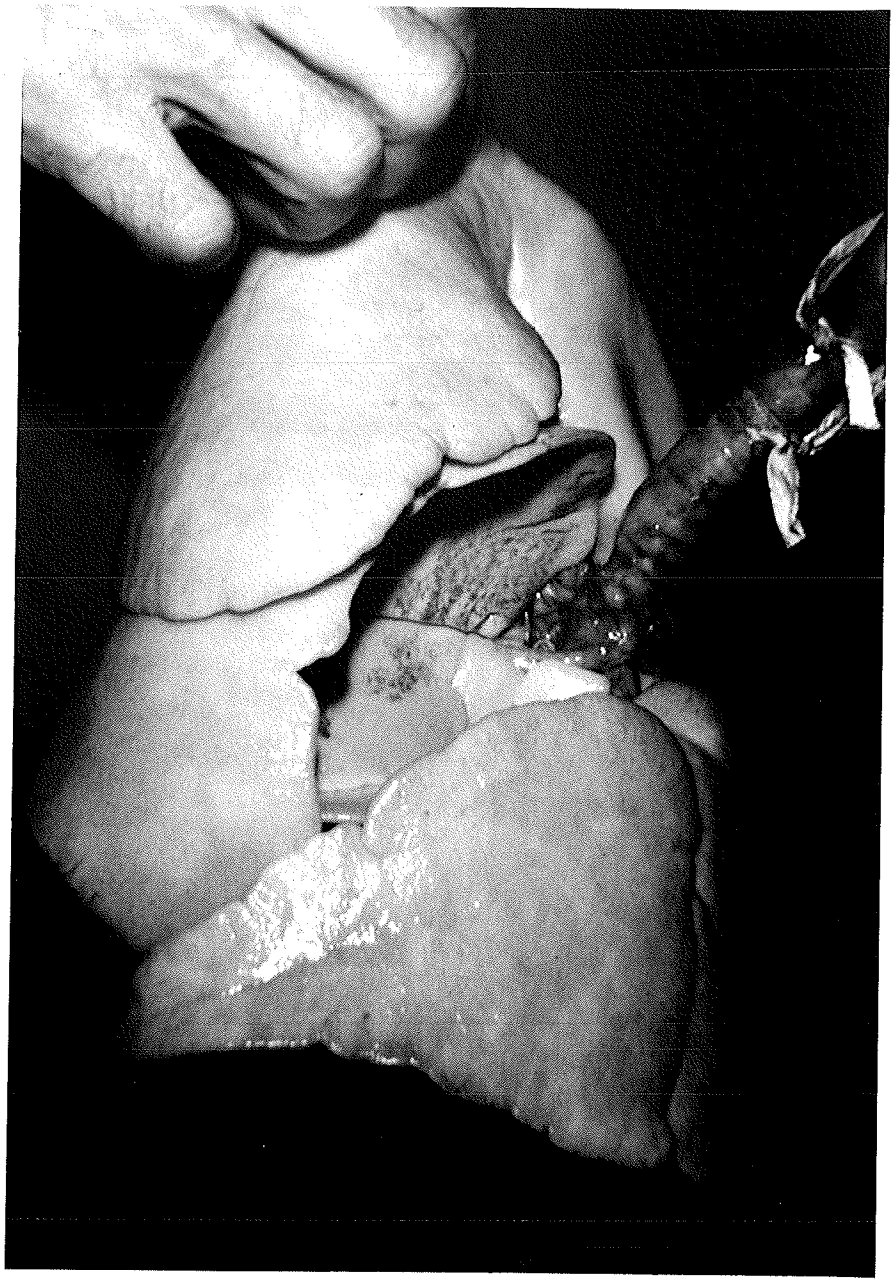

Figure 2: Photograph of an excised right lung following postpneumonectomy compensatory growth; medial aspect showing large, displaced cardiac lobe.

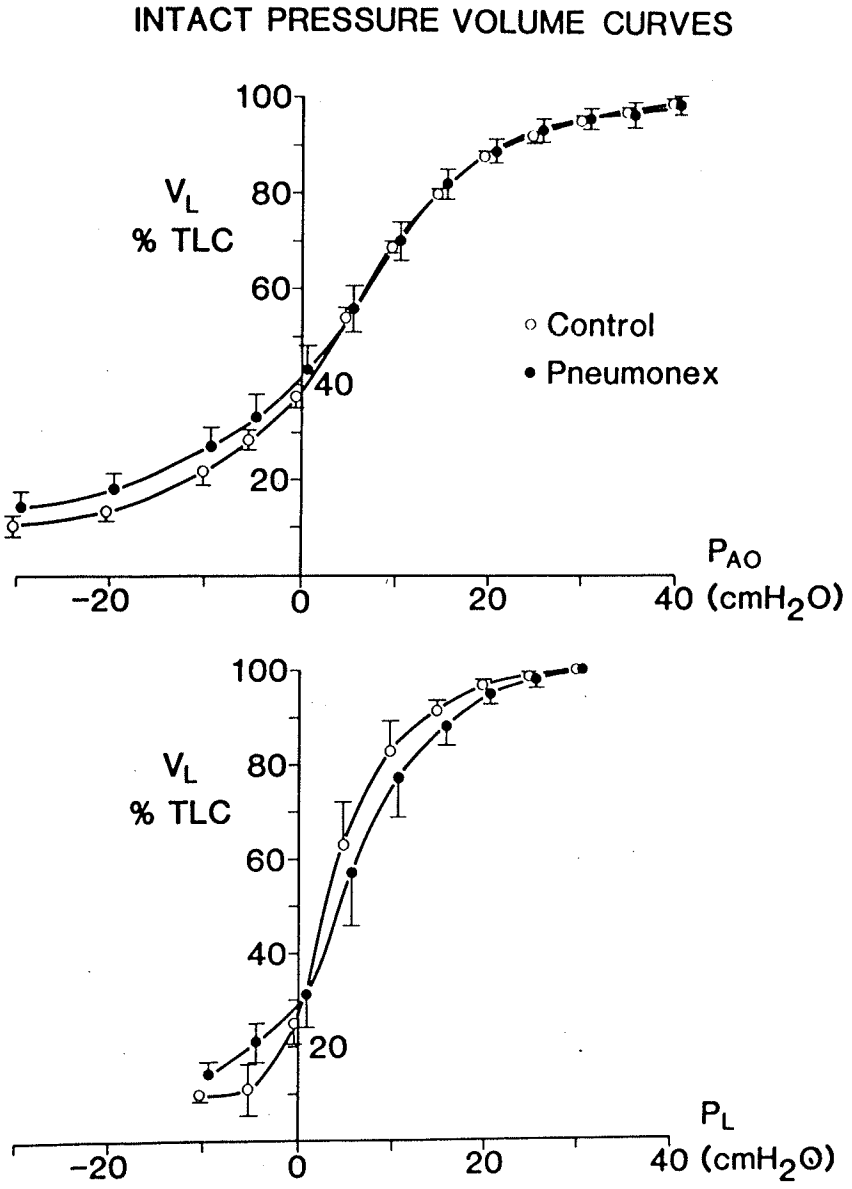

Figure 3: Intact static pressure-volume curves comparing control and pneumonectomized dogs. Volume of the lung as percent TLC is plotted on the ordinate. Upper panel shows the P-V curve of the entire respiratory system with P_{AO} plotted on the abscissa. Lower panel is the P-V curve of the lung with transpulmonary pressure plotted on the abscissa.

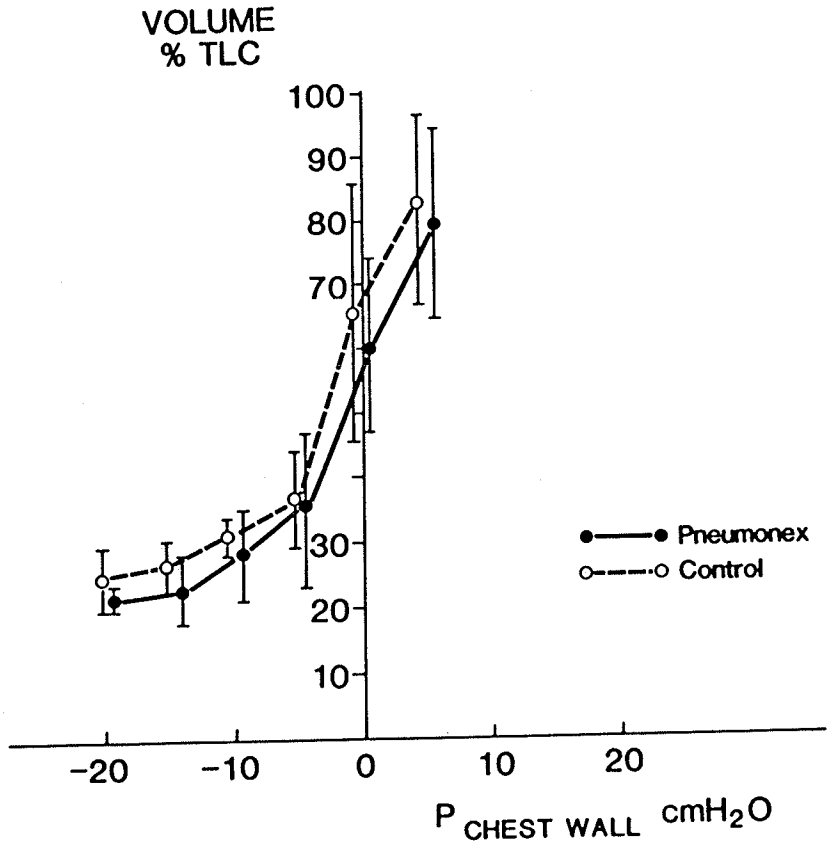

Figure 4: Computed pressure-volume curve of the chest wall comparing control and pneumonectomized dogs. Volume as percent TLC is shown on the ordinate, chest wall pressure on the abscissa.

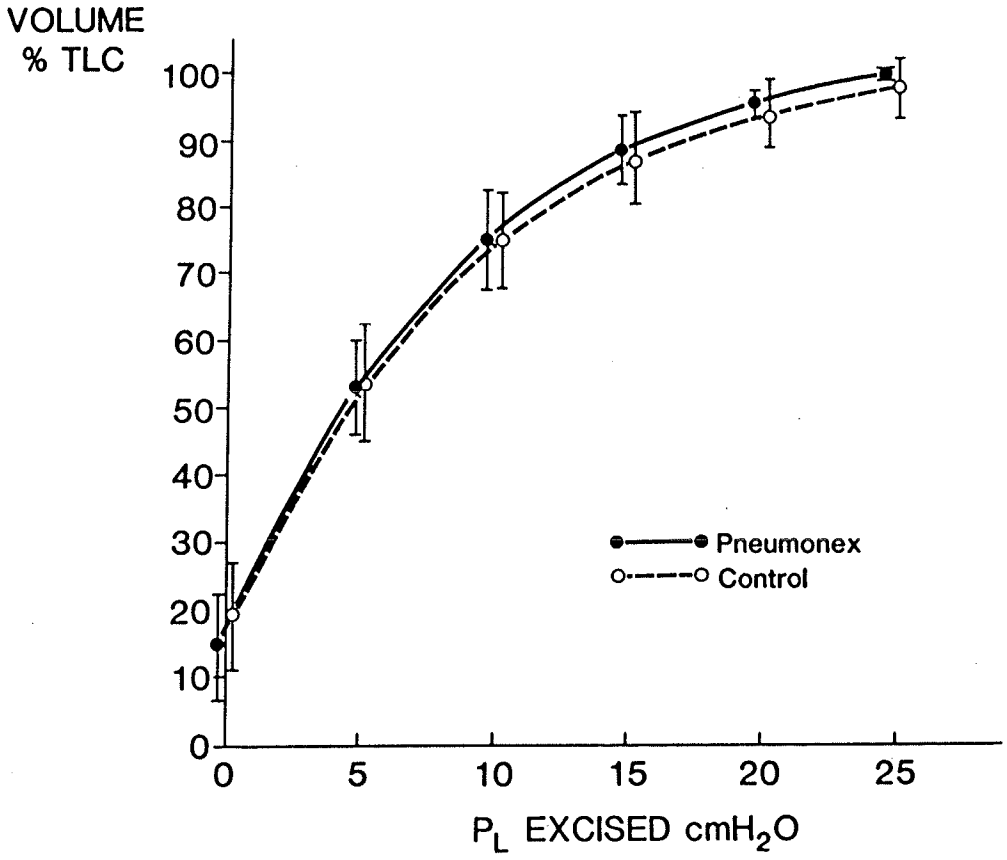

Figure 5: Pressure-volume curves of the excised lung comparing control and pneumonectomized dogs. Volume as percent TLC is on the ordinate, excised lung pressure on the abscissa.

air and 80% Helium - 20% Oxygen (HeO_2) are presented in Figure 6. Not all of the peak flow values were available in all cases as indicated by the interrupted graphs. The mean flow-volume curve on room air is greatly reduced in the pneumonectomized animals at all lung volumes. When breathing HeO_2, maximum expiratory flow increased above that measured during room air breathing, but the values in pneumonectomized dogs were still greatly reduced compared to that of control animals. We are interested in the flow events at 25% and 50% of VC ($\dot{V}max_{25}$ and $\dot{V}max_{50}$, Table III). In control animals $\dot{V}max_{25}$ was 3.71 $\pm$ 0.49 l/s on room air, compared with 1.41 $\pm$ 0.13 l/s for pneumonectomized animals. There is a similar decrease in $\dot{V}max_{50}$ which averaged 2.54 $\pm$ 0.30 l/s in P dogs while it was 6.03 $\pm$ 0.50 l/s in controls. Similar large differences in flow were seen when dogs were breathing the helium-oxygen gas mixture. On HeO_2, $\dot{V}max_{25}$, was 6.43 $\pm$ 0.77 l/s in controls compared with 2.26 $\pm$ 0.22 l/s for group P, a decrease of 65%. $\dot{V}max_{50}$ was 62% less in pneumonectomized puppies than in control animals, $\dot{V}max_{50}$ averaged 10.4 $\pm$ 0.59 l/s for C and 3.91 $\pm$ 0.47 l/s for P. The helium response, the percent increase in flow while breathing HeO_2 compared to air was not different between the two groups. At 25% VC the helium response was a 55.8 $\pm$ 6.35% increase in flow for group C compared to a 58.3 $\pm$ 2.0% increase in flow for pneumonectomized dogs. A similar pattern was seen at 50% VC with a 60.2 $\pm$ 9.12% increase for C and 53.2 $\pm$ 5.72% increase for P.

Regional respiratory system compliance was studied using slowly inhaled boluses of ^{133}Xenon gas. These mean results are shown in Figure 7, which compares right and left hemithoraces.

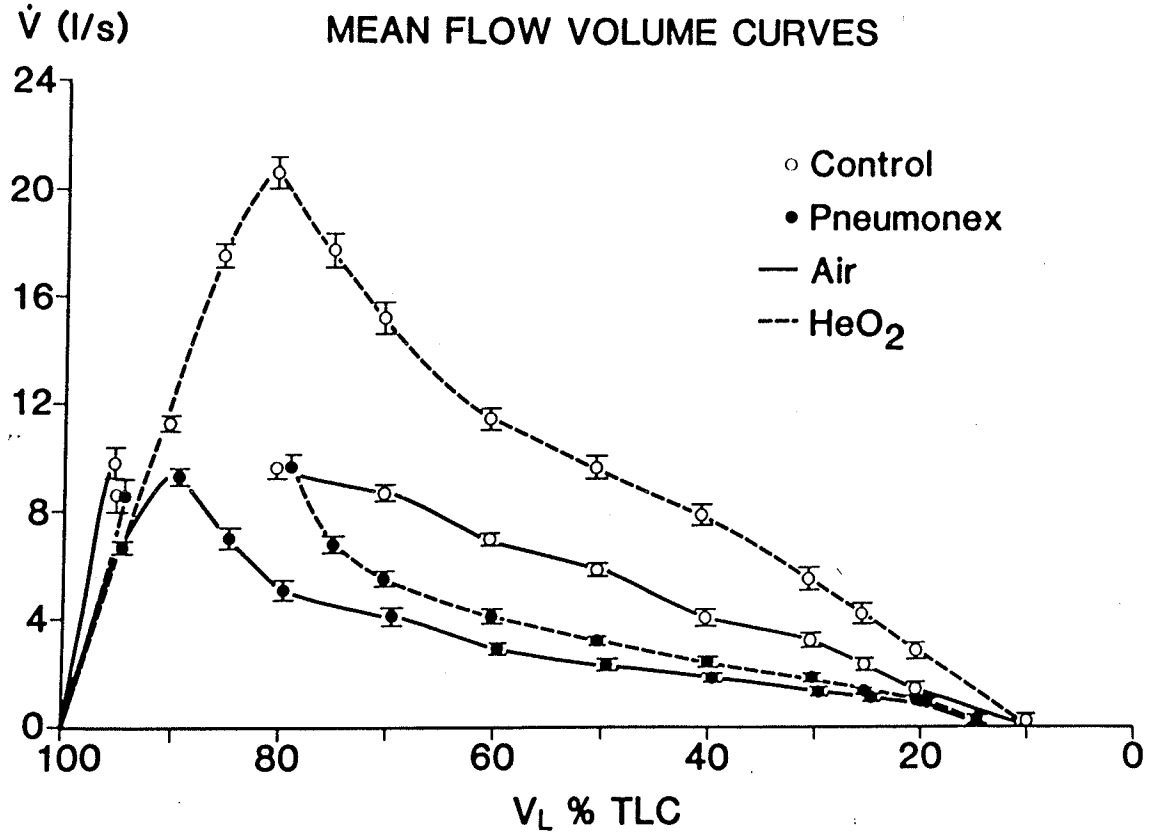

Figure 6: Mean flow-volume curves comparing control and pneumonectomized dogs when breathing air (——) and 80%He-20%O_2 (– – –). Flow in litres per second is plotted on the ordinate and volume as percent TLC is on the abscissa.

TABLE III

		CONTROL			PNEUMO		
		Air	HeO_2	%	Air	HeO_2	%
$\dot{V}max_{25}$	$\bar{X}$	3.71	6.43	55.8	1.41	2.26	58.3
	SEM	0.49	0.77	6.35	0.13	0.22	2.0
	n	8	6	6	8	7	7
$\dot{V}max_{50}$	$\bar{X}$	6.03	10.4	60.2	2.54	3.91	53.2
	SEM	0.50	0.59	9.12	0.30	0.47	5.72
	n	8	6	6	8	7	7

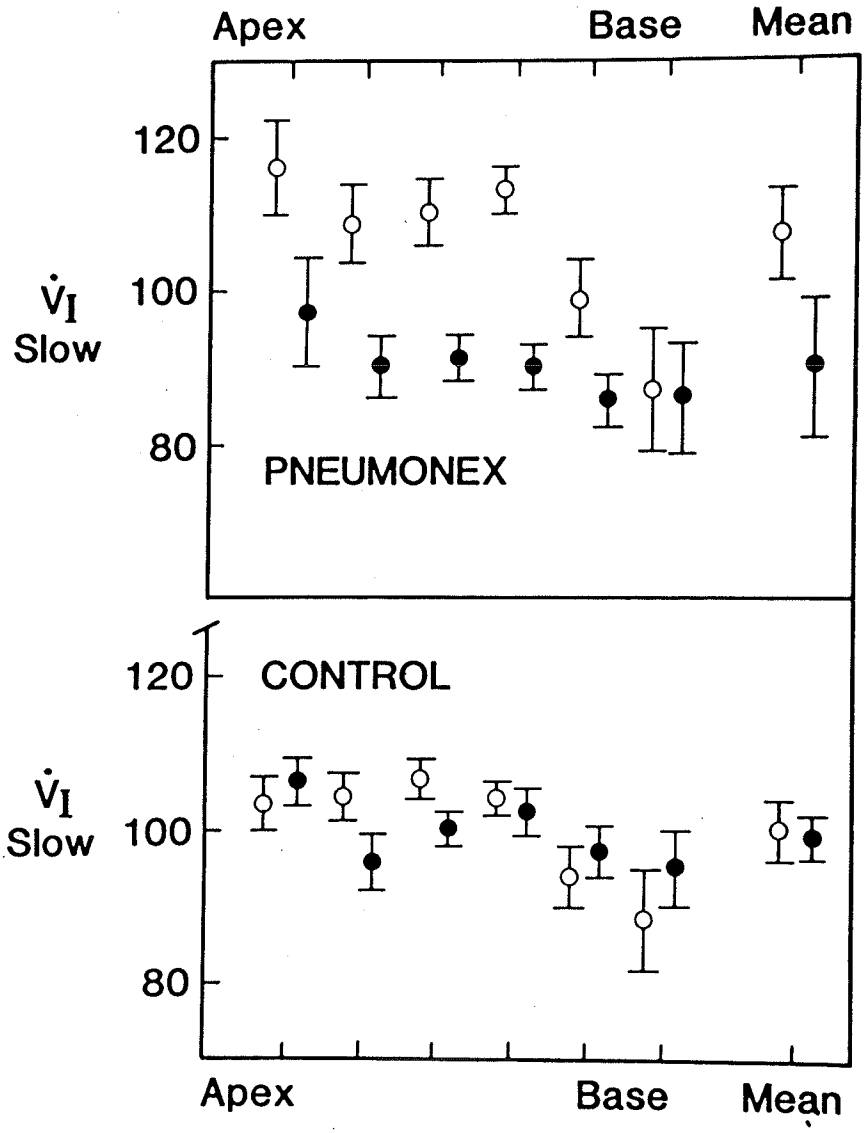

Figure 7: Effect of pneumonectomy on regional respiratory compliance. Open circles represent counts from the right hemithorax and closed circles represent the left hemithorax. $\dot{V}_I$ slow on the ordinate is the regional distribution of a slowly inhaled bolus indexed for unit volume and plotted as a function of distance down the lung. The mean indices are shown at the right.

The output of the six regional counters in the control dogs, lower panel, shows that there was equal distribution of the radioactive bolus to each side of the chest. However in the upper panel it may be seen that there was unequal distribution of the bolus in pneumonectomized animals. More of the gas went to the right side of the thorax, indicating that the compliance was decreased in the left hemithorax, particularly towards the apex.

Figure 8 indicates the distribution of a rapidly inhaled bolus of xenon gas. This is a reflection of alterations in regional airway resistance. Again from the lower panel, representing control dogs, it is apparent that the bolus was evenly distributed between the left and right hemithorax, and between the apex and base. The upper panel, pneumonectomized dogs, demonstrates that there was an alteration in the resistance during compensatory growth. More of the bolus went to the right hemithorax, suggesting that the resistance was greater on the left side.

Distribution of perfusion is outlined in Figure 9. There is an equal distribution of perfusion to each hemithorax in control studies as shown in the lower panel. The upper panel demonstrates that there is an alteration in perfusion distribution with pneumonectomy. There is decreased blood flow to the left hemithorax.

Regional distribution of volume as a percent of total count rate is shown in Figure 10. This demonstrates that regional volume increases from apex to base in both control and pneumonectomized dogs and is evenly distributed between the right and left sides in control animals. However in pneumonectomized

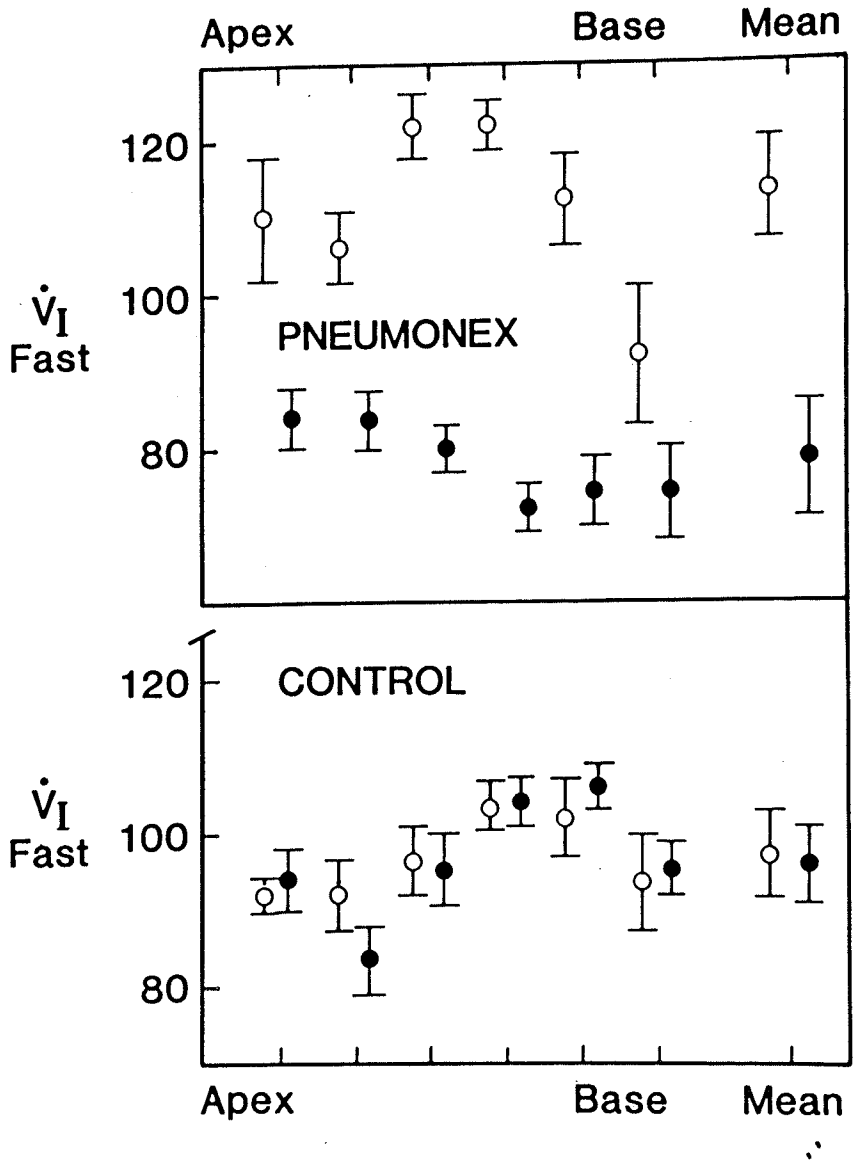

Figure 8: Effect of pneumonectomy on regional airway resistance. Count rates following the rapid inhalation of xenon are indexed per unit volume on the ordinate and plotted as a function of distance down the lung. The mean value of all six counters is also shown.

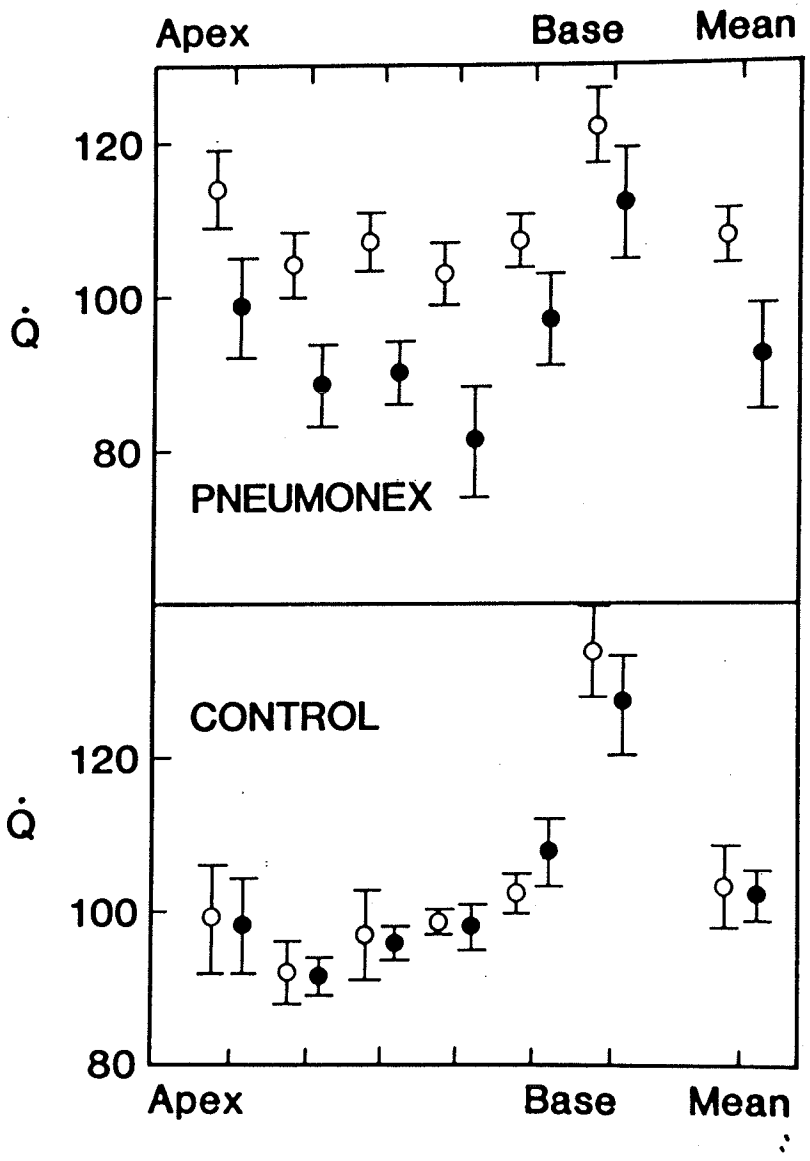

Figure 9: Perfusion distribution at FRC in control and pneumonectomized dogs; open circles represent indices for the right hemithorax and closed circles represent the left hemithorax. $\dot{Q}$ is the perfusion/unit volume as a function of distance down the lung. The mean index is also shown.

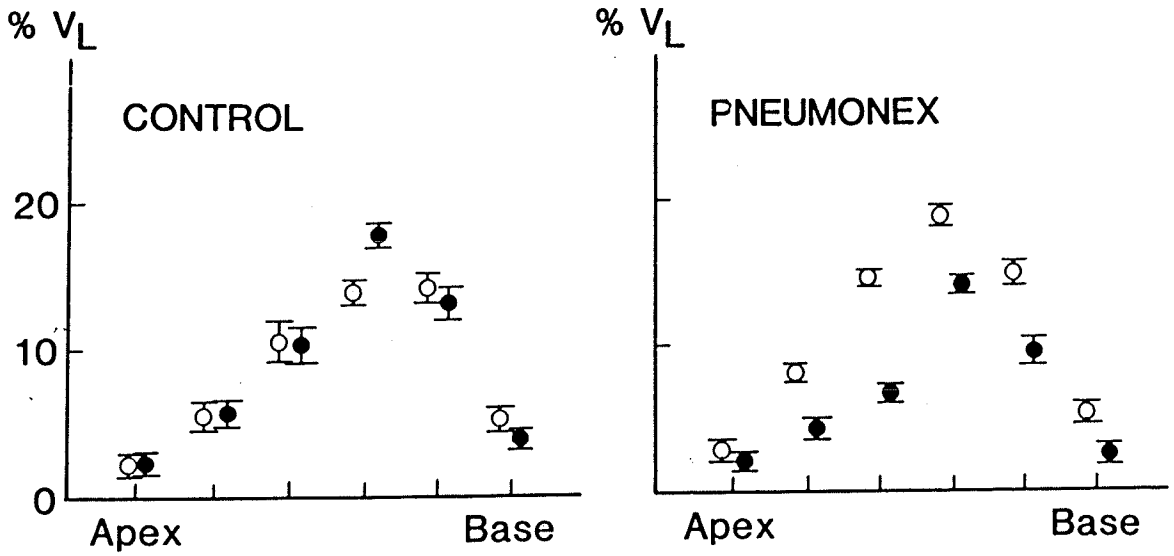

Figure 10: Effect of pneumonectomy on regional count rates at equilibration. Regional ventilation as a percent of total lung volume is shown as a function of distance down the lung. Open circles: right hemithorax; closed circles: left hemithorax.

dogs there is decreased regional volume in the left hemithorax as a percent of the total.

IV. DISCUSSION

Removal of the left lung in 10 week old dogs resulted in great compensatory growth of the contralateral lung. The volume, in terms of TLC, and the weight of the remaining lung at 25 weeks equalled the volume and weight of both lungs in control animals. In vivo TLC agreed well with TLC measured in vitro and was the same per unit body weight in pneumonectomized and control dogs. Similar responses have been demonstrated by many authors in various animal models (1,2,4-14,31,32,34-39). We are not able to acertain whether this growth is indicative of true alveolar multiplication and/or an increase in alveolar size. However, we did not find any major abnormalities in the static mechanical properties or behavior of the adaptive lung, which leads us to believe that there was accelerated growth and alveolar multiplication in the remaining lung of pneumonectomized dogs. Thurlbeck et al.(13), using dogs under precisely the same conditions, found an increase in the alveolar surface area proportional to the increase in volume which they interpreted to mean an increased alveolar surface complexity brought about by the formation of new alveoli. There was also an increased number of alveoli per ml. of tissue in the adapted lung and a trend to increase the alveolar duct proportion compared to control animals. Due to the similarities in experimental protocol, we believe that these results probably applied to our animals.

We found that there was a significant increase in the weight of all lobes of the contralateral lung in pneumonectomized puppies, but that this increase was greatest in the cardiac lobe.

Various types of lobar growth have been previously described. Thurlbeck and coworkers (13) suggested that the adaptive response was greatest in the lower lobe, since the inter-alveolar wall distance was less in this lobe. Davies et al.(14) suggest, on the basis of increased alveolar density, that the diaphragmatic (cardiac) lobe may be more responsive than other lobes. This is in agreement with our observations of lobar weight. The increased adaptive growth in the cardiac lobe may be the result of increased stresses placed on the tissue. After pneumonectomy one might expect more growth in lobes adjacent to mediastinal defects, since they may be exposed more directly to negative pressures from the opposite hemithorax and they would not have to displace the mediastinum during growth. The cardiac lobe (Fig. 2) appeared to grow through the mediastinum and into the left hemithorax, so it is likely that it was adjacent to a mediastinal defect. Other lobes, which grew less, appeared to do so by displacing the mediastinum.

We found a slight increase in FRC/TLC and a significant increase in RV/TLC postpneumonectomy. Ford et al.(21) found a slight, but significant increase in both FRC/TLC and RV/TLC in pneumonectomized dogs compared to sham operated controls. Wilcox et al.(15) found no change in FRC/TLC following pneumonectomy in dogs operated at 6 to 10 weeks of age compared to unoperated controls. Yee and Hyatt (35), using an intact rabbit model, found a reduction of the forced vital capacity (FVC), which was due to an increased RV. McBride et al.(31) described a similar response following lung resection in patients at an early age, however they were not certain of the extent of compensatory growth.

Static lung volumes are determined by the lung elastic recoil of the lung and chest wall and in the case of RV, we measured it by

determining the amount of airway closure. We found no difference in the excised trapped gas volume between pneumonectomized and control dogs, a finding confirmed by Ford et al.(21) using a slightly different technique. This indicated that airway closure was the same in control and pneumonectomized animals. Buhain and Brody (5) found evidence of airtrapping below 5 cm H_2O P_L in excised rat lungs, but differences in species and experimental technique may account for this conflict.

Small differences in mechanical properties of the postpneumonectomy lung resulting in larger FRC/TLC and RV/TLC could not be explained on the basis of alterations in TLC or the static recoil of the lungs either in our series or that of Ford et al.(21). The latter concluded that the larger FRC and RV following pneumonectomy must be a reflection of alterations in chest wall mechanics, so that at these lung volumes the outward recoil of the chest wall was increased. We would expect to find increased RV/TLC and FRC/TLC immediately following surgery when the remaining lung is mainly in the right hemithorax, but by 25 weeks of age the right remaining lung was the same weight and volume as both lungs of control animals, and the cardiac lobe filled the left hemithorax. However it is possible that the fit of the lung and chest wall was not normal. The lung had been placed under mechanical stress and adaptive growth stimulated, but it is likely that this growth was limited by the mediastinum and its contents so that the postpneumonectomy lung probably matched the thoracic cavity less well than in control animals. This mismatching of shape of lung and chest wall may have caused the increased RV/TLC we observed, since it could not be explained by changes of TLC or alterations in the static elastic recoil of the lung. We were unable to find any

difference in the static elastic recoil of the chest wall between pneumonectomized and control dogs, at any lung volume. However, our method of measuring chest wall recoil necessarily assumed that pleural pressure was uniform and equal to what we measured or calculated. If alterations in lung volume were due to inhomogeneities of pleural pressure, as would be the case when the lung and chest wall did not fit, our techniques of assessing chest wall recoil would not be appropriate.

We found no significant difference in the lung static elastic recoil between control and pneumonectomized dogs. Ford et al.(21) using an identical protocol, found that pneumonectomized dogs appeared to have stiffer lungs with reduced compliance and increased elastic recoil. This was true for measurements made both in vivo and in vitro, but the differences while significant, were small. It is possible that similar changes did occur in our dogs, but due to the variability of the static pressure-volume curves this was not evident. The measurement of esophageal pressure as an estimation of pleural pressure is extremely sensitive to alterations in body position and the shift in the mediastinum following pneumonectomy may have altered the pressure measurement.

Compliance of the respiratory system, as measured with the slow inhalation of xenon gas, was altered in pneumonectomized dogs. Compliance of the left hemithorax was reduced from that on the right side. Perhaps this was the result of incomplete adaptive growth. A reduction in compliance may be due to alterations in the lung, such as a reduction in the number of elastic units present and/or a change in the compliance of the chest wall. At FRC, where compliance was measured, we found no differences in the static elastic recoil of the intact lung or chest wall. We also found no

difference in the excised static elastic recoil of the lung, but in this case the P_L was the same for all lung units. Perhaps the change in compliance is due to a difference is transpulmonary pressure between the right and left hemithorax in vivo. Ford et al.(21) found differences in regional distribution of volume with an increased FRC/TLC at the left lung base compared to the right in pneumonectomized dogs. On the basis of Ford et al.'s data, one would predict a reduced compliance at the left base, due to relative overexpansion of lung units. We did not find this pattern, but rather a uniform decrease in the compliance in the entire left hemithorax in pneumonectomized dogs. We can not be certain, but perhaps our measurements were more sensitive and allowed us to see small decreases in the volume distribution to the upper left side. The reduced compliance of the left hemithorax following pneumonectomy may be due to an increase in transpulmonary pressure or increased lung volume on that side due to a poorer fit between the adapted lung and the chest wall.

Using a rapidly inhaled bolus of xenon gas, we found that airway conductance was decreased in the left hemithorax which presumably contained lung tissue that had undergone compensatory growth. This measurement is probably due largely to increased airway resistance (R_{AW}) in the left hemithorax. The volume of the lung is similar in both control and pneumonectomized dogs and therefore will not account for differences in airway conductance. Increased airway resistance occurs when the airways grow much less than the parenchyma following pneumonectomy, so that the airway cross-sectional area is much smaller than normal. Boatman (8) and Yee and Hyatt (31) using bronchograms in pneumonectomized rabbits, report that adapted airways do not increase in diameter.

Pimmel et al.(18) measured dynamic oscillatory resistance in postpneumonectomized dogs at 3 years of age, and found it slightly, but not significantly increased compared to controls. They also found that FRC was not different between control and pneumonectomized dogs and suggested that there had been some adaptation in the lung mechanical properties. Perhaps there was adaptation of the airways following pneumonectomy but this process was much slower than lung tissue growth and is therefore not evident in our dogs.

Yee and Hyatt (31), using the Mead-Whittenberger technique (35), measured pulmonary resistance in pneumonectomized rabbits. They found that pulmonary resistance while breathing air was significantly increased postpneumonectomy, being 1.7 times control. Our regional ventilation results can not account for this increase. ^{133}Xe concentrations on the right hemithorax averaged 137% of those in the left after bolus inhalation (Fig.8), suggesting that volume-weighted resistance on the left was 137% that on the right. With approximately 40% of the lung in the left hemithorax (Fig.10), our results predict that the regional changes we observed would increase overall resistance by some 15%. This is a plausible underestimate because regional resistances do not take into account the fact that in pneumonectomized dogs the number of major bronchi- mainstem and lobar airways- is approximately halved.

There was a striking reduction in $\dot{V}max_{25}$ and $\dot{V}max_{50}$ following pneumonectomy. Maximum expiratory flow is determined by three factors. Lung recoil determines the driving pressure (alveolar pressure - pleural pressure). Airway resistance upstream from the point of flow limitation determines frictional pressure losses and luminal pressure at the site of flow limitation. Thirdly, the

airway compliance at the site of flow limitation may alter maximum flow. If the airways collapse when exposed to small negative transmural pressures, flow will be limited whatever the elastic recoil or state of upstream airways. Since lung elastic recoil was normal in our dogs postpneumonectomy, the decrease in flow they demonstrated must have been due to increased airway resistance. Wave speed theory (33,41) states that maximum expiratory flow becomes limited at a point in the airway when flow velocity equals the speed of propagation of pressure pulse waves. Each point along the airway has a tube wave speed, the critical value of which is determined by the physical characteristics of the tube (cross-sectional area and compliance) and the density of the gas:

$$\dot{V}_{max} = (A^3 \times dB/dA \times 1/\rho q)^{.05}$$

where q is a correction factor for departure from blunt velocity profile, ρ is the density of the gas, A is the area of the airway, and dB/dA is the compliance of the airway, B representing the airway transmural pressure. The site of flow limitation occurs at a given flow when the value of $A^3 \times dB/dA$ reaches a minimum at some point along the airway. $\dot{V}_{max}$ is determined by the forces driving the airflow and the limiting cross-sectional area of the airway. The driving force between alveoli and intrathoracic airway loci where flow becomes limited is the lung elastic recoil pressure (P_{el}). The luminal airway pressure, which combined with pleural pressure, determines the cross-sectional area of the airway, is the sum of frictional (P_{FR}) and convective accelerative (P_{CA}) pressure losses. Thus for a given airway at a given P_{pl}, $\dot{V}_{max}$ is determined by $P_{el} - (P_{FR} + P_{CA})$.

The reduction in $\dot{V}_{max}$ postpneumonectomy did not arise from a

decrease in P_{el} since elastic recoil is normal. However (P_{FR} + P_{CA}) increased greatly. P_{CA} increased as a normal lung volume of air was expelled from the remaining right lung through one mainstem bronchus. P_{FR} also increased because the length of the remaining airways increased as the right lung grew into the left hemithorax. The reduced flow could also arise from alterations in the airway geometry, resulting in decreasing A or increasing dB/dA. Since we did not alter the properties of the airway, we propose that the flow limiting segment has moved peripherally. As the site of flow limitation moves peripherally, the area of the airway, A, will increase and the airway compliance, dB/dA, will decrease. However, in a pneumonectomized dog A will increase far less than a normal dog as the site of flow limitation moves out. Thus A^3 x dB/dA will be much less than normal and $\dot{V}_{max}$ greatly reduced.

Our report of a large reduction in MEFV curves following pneumonectomy is consistent with the work of others. Yee and Hyatt (35) studying pneumonectomized rabbits, also report decreases in maximal expiratory flow. Although their results were similar, we found a greater reduction in flow at $\dot{V}max_{25}$ and $\dot{V}max_{50}$. Yee and Hyatt found that flow was reduced to 66% of control following pneumonectomy, while our dogs averaged 42% of control. We were not able to correlate the fall in $\dot{V}max_{50}$ post-pneumonectomy to the changes in airway conductance determined by the xenon studies. This is evidence that the alteration is not a regional change in airway conductance.

$\Delta\dot{V}$max, the percent increase of $\dot{V}max_{50}$ on helium over that on air, was similar in both control and pneumonectomized dogs. The large increase in airflow when breathing HeO_2 is indicative of central airways obstruction. According to wave speed theory, the effect of

gas density on $\dot{V}_{max}$ depends not on the site of flow limitation, but on the ratio of:

$$\frac{P_{FR}}{P_{FR}+P_{CA}} = \frac{P_{FR}}{P_{TOT}}$$

We found a reduction in $\dot{V}max_{25}$ and $\dot{V}max_{50}$ which would indicate movement of the flow limiting site, so that P_{FR} increases. However, the similar response to less dense HeO_2 gas seen in both control and pneumonectomized dogs would suggest that P_{FR} increased as much as P_{TOT} following surgery. We would suggest that the site of flow limitation has moved only slightly towards the periphery. Yee and Hyatt (31) report similar finding in pneumonectomized rabbits. They found that flows in the treated group were 62% of control while breathing HeO_2 and 66% of control while breathing air.

The adaptive response of the pulmonary circulation following pneumonectomy has been reported elsewhere. Kato et al.(18), studying 13 pneumonectomized pups, reported no significant increase in mean pulmonary artery pressure (PAP) either immediately following surgery or over a 16 week recovery period. However Rudolph et al.(19), studying 8 pups with a left pneumonectomy, partial or complete left pulmonary artery ligation, found a 240% rise in mean PAP over control immediately post surgery with a continual slow increase over the next few months. In 2 dogs there was a decrease in PAP many months later which may be due to hyperplasia with an increase in the total number of blood vessels or distension of small pulmonary vessels or due to an improvement in histological features. Davies et al.(14) did not find any changes in the mean percent medial thickness (%MT), an indication of muscularization of vessels. In 4 animals having a left pneumonectomy at an early age, there was no difference from controls in preacinar or intra-acinar arterial

%MT when studied five years later. This was true for vessels supplying the alveolar wall, alveolar duct or the respiratory bronchiolus. The lobar values of %MT were also similar.

Maisson and Schilling (20) found that FRC decreased while blood flow increased with a net gain in gas exchange per unit tissue representing a compensation for loss of parenchyma when the upper lobes were removed in young dogs. The lower lobes are favored by hydrostatic filling and may receive a larger share of the blood flow by opening collateral capillaries or through vasodilation. Our pneumonectomized dogs demonstrated a reduction in perfusion to the left hemithorax. We suggest that there is an alteration in the perfusion of the adapted lung, particularly to the cardiac lobe which has undergone the most compensatory growth. Tissue in the left hemithorax is receiving less blood per unit volume compared to tissue in the right hemithorax as the pulmonary vessels are now elongated and narrower.

Following pneumonectomy at an early age there is much compensatory growth. The parenchyma grows so that the weight and volume of the remaining lung equals that of both lungs in control animals. Although the volumes and static mechanics of lungs may appear normal, the dynamic function is severely impaired. Airflow is greatly reduced. We believe that the compensatory growth of the airways and pulmonary circulation has not kept pace with the adaptive growth of the parenchyma. This is an example of extreme dysynaptic growth. This study suggests that after resection of damaged lung tissue in young patients, function of the remianing lung will be abnormal even if there is compensatory growth.

V. BIBLIOGRAPHY

1. Thurlbeck, W.M. Postnatal growth and development of the lung. Am. Rev. Resp. Dis. 111:803-844, 1975.

2. Burri, P.H. and S. Sehovic. The adaptive response of the rat lung after bilobectomy. Am. Rev. Resp. Dis. 119:769-777, 1979.

3. Fishman, A.P., ed. Pulmonary Diseases and Disorders McGraw-Hill Book Co. New York. Chapter 19, J.S. Brody, pp. 304-314, 1980.

4. Brody, J.S., R. Burki and N. Kaplan. Deoxyribonucleic acid synthesis in lung cells during compensatory lung growth after pneumonectomy. Am. Rev. Resp. Dis. 117:307-316, 1978.

5. Buhain, W.J. and J.S. Brody. Compensatory growth of the lung following pneumonectomy. J. Appl. Physiol. 35(6):898-902, 1973.

6. Das, R.M. and W.M. Thurlbeck. The events in the contralateral lung following pneumonectomy in the rabbit. Lung. 156:165-172, 1979.

7. Cowan, M.J. and R.G. Crystal. Lung growth after unilateral pneumonectomy: quantitation of collagen synthesis and content. Am. Rev. Resp. Dis. 111:267-277, 1975.

8. Boatman, E.S. A morphometric and morphological study of the lungs of rabbits after unilateral pneumonectomy. Thorax. 32:406-417, 1977.

9. Holmes, C. and W.M. Thurlbeck. Normal lung growth and response after pneumonectomy in rats at various ages. Am. Rev. Resp. Dis. 120:1125-1136, 1979.

10. Langston, C., P. Sachdeva, M. Cowan, J. Haines, R. Crystal and W.M. Thurlbeck. Alveolar multiplication in the

contralateral lung after unilateral pneumonectomy in the rabbit. Am. Rev. Resp. Dis. 115:7-13, 1977.

11. Nattie, E.E., C.W. Wiley and D. Bartlett. Adaptive growth of the lung following pneumonectomy in rats. J. Appl. Physiol. 37(4):491-495, 1974.

12. Sery, Z., E. Keprt, M. Obrucnik. Morphometric analysis of late adaptation of the residual lung function following pneumonectomy in young and adult rabbits. J. Thoracic and Cardiovas. Surg. 57:549-557, 1969.

13. Thurlbeck, W.M., W. Galaugher, J. Mathers. Adaptive response to pneumonectomy in puppies. Thorax. 36:424-427, 1981.

14. Davies, P., J. McBride, G. Murray, B. Wilcox, J. Shallal and L. Reid. Structural changes in the canine lung and pulmonary arteries after pneumonectomy. J. Appl. Physiol. 53(4):859-864, 1982.

15. Wilcox, B.R., G.F. Murray, M. Friedman and R.L. Pimmel. The effects of early pneumonectomy on the remaining pulmonary parenchyma. Surgery. 86:294-300, 1979.

16. Reid, L.M. The pulmonary circulation: Remodeling in growth and disease. Am. Rev. Resp. Dis. 119:531-546, 1979.

17. Meyrick, B. and L. Reid. Pulmonary arterial and alveolar development in normal postnatal rat lung. Am. Rev. Resp. Dis. 125:468-473, 1982.

18. Kato, H., L. Kidd and P.M. Olley. Effects of hypoxia on pulmonary vascular reactivity in pneumonectomized puppies and minipigs. Circ. Research. 28:397-402, 1971.

19. Rudolph, A., E. Neuhauser, R. Golinko and P. Auld. Effects of pneumonectomy on pulmonary circulation in adult and young animals. Circ. Research. 9:856-861, 1961.

20. Massion, W.H. and J.A. Schilling. Physiological effects of lung resection in adult and puppy dogs. J. Thoracic and Cardiovas. Surg. 48:239-250, 1964.

21. Ford, G.T., W. Galaugher, L. Forkert, J.A. Fleetham, W.M. Thurlbeck and N.R. Anthonisen. Static lung function in puppies after pneumonectomy. J. Appl. Physiol. 50(6):1146-1150, 1981.

22. Petit, J.M. and G. Milic-Emili. Measurement of endoesophageal pressure. J. Appl. Physiol. 13:481-484, 1958.

23. DuBois, A., S. Botelho and J.H. Comroe. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. J. Clin. Invest. 35:328-335, 1956.

24. Bedell, G.N., R. Marshall, A. DuBois and J.H. Comroe. Plethysmographic determination of the volume of gas trapped in the lungs. J. Clin. Invest. 35:664-670, 1956.

25. DuBois, A., S. Botelho, G. Bedell, R. Marshall and J. Comroe. A rapid plethysmographic method for measuring thoracic gas volume: A comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J. Clin. Invest. 35:322-326, 1956.

26. Anthonisen, N.R., L.J. Peress, D.I. Siegler and S. Dhingra. Lung volume, volume history and the distribution of inhaled boluses. Resp. Physiol. 33:279-288, 1978.

27. Robertson, P.C., N.R. Anthonisen and D. Ross. Effect of inspiratory flow rate on regional distribution of inspired gas. J. Appl. Physiol. 26(4):438-443, 1969.

28. Romano, A. Applied Statistics for Science and Industry

pp.86-89, 148-160. Allyn and Bacon Inc. Boston, 1977.

29. Macklem, P.T. Procedures for standardized measurements of lung mechanics. National Heart and Lung Institute, Division of Lung Diseases. Bethesda, Md., 1974.

30. Keppel, G. Design and Analysis: A Researcher's Handbook. pp.433-442. Prentice-Hall Inc. New Jersey, 1973.

31. McBride, J.T., M.E. Wohl, D.J. Strieder, A.C. Jackson, J.R. Morton, R.G. Zwerdling, N.T. Griscom, S. Treves, A.J. Williams and S. Schuster. Lung growth and airway function after lobectomy in infancy for congenital lobar emphysema. J. Clin. Invest. 66:962-970, 1980.

32. Pimmel, R., M. Friedman, G. Murray, B. Wilcox and P. Bromberg. Forced oscillatory resistance and compliance parameters following pneumonectomy in beagle dogs. Respiration. 41:17-24, 1981.

33. Ingram, R.H. and E.R. McFadden. Localization and mechanisms of airway responses. New Eng. J. Med. 297:596-600, 1977.

34. Pimmel, R.L., M. Friedman, G.F. Murray, B.R. Wilcox and P.A. Bromberg. Forced oscillatory resistance and compliance parameters following pneumonectomy in beagle dogs. Respiration. 41:17-24, 1981.

35. Yee, N.M. and R.E. Hyatt. Effect of left pneumonectomy on lung mechanics in rabbits. Accepted for publication in J. Appl. Physiol.

36. Wohl, M.E., N. Thorne, D. Strieder, S. Schuster, S. Treves and R.G. Zwerdling. The lung following repair of congenital diaphragmatic hernia. J. Pediatrics. 90(3):405-414, 1977.

37. Brody, J.S. Time course of and stimuli to compensatory growth

of the lung after pneumonectomy. J. Clin. Invest. 56:897-904, 1975.

38. Rienhoff, W., F.L. Reichert and G.J. Heuer. Compensatory changes in the remaining lung following total pneumonectomy. The Johns Hopkins Hospital Bulletin. 57:373-383, 1935.

39. Ryland, D. and L. Reid. Pulmonary aplasia - a quantitative analysis of the development of the single lung. Thorax. 26:602-609, 1971.

40. Leith, D.E. and J. Mead. Principles of body plethysmography. National Heart Lung Institute, Division of Lung Diseases. Bethesda, Md., 1974.

41. Despas, P.J., M. Leroux and P.T. Macklem. Site of airflow obstruction in asthma as determined by measuring maximal expiratory flow breathing air and a helium-oxygen mixture. J. Clin. Invest. 51:3235-3243, 1972.

42. Mink, S.N., M. Ziesmann and L.D.H. Wood. Mechanisms of increased maximum expiratory flow during HeO_2 breathing in dogs. J. Appl. Physiol. 47(3):490-502, 1972.

43. Geddes, L.A. and L.E. Baker. Principles of Biomedical Instrumentation. pp.58-62. John Wiley and Sons Inc. New York, 1968.