PROBLEMS ASSOCIATED WITH THE OPERATION OF PNEUMONECTOMY

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by

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ILLUSTRATIONS

PREFACE

This manuscript is the product of two years of research conducted at the Experimental Surgical Laboratories of McGill University. The investigations were carried out over this period because it was desirable in one of the studies to have the pneumonectomized animals survive for as many months as possible.

I am indebted to Dr. D. E. Ross who suggested the problem of the fate of the remaining lung. When the literature pertaining to this was reviewed other problems which could be investigated at the same time were encountered. These were the bronchial stump and intrathoracic readjustments. Much has been written on each of these problems but there has been no unanimity of opinion. Thus any additional contribution is valuable.

The history of pulmonary surgery was partially revealed when the many publications were read. This subject was most interesting so an attempt was made to complete the story. A brief outline of it has been included in this manuscript. Unfortunately in assembling this it has been necessary in many instances to quote from publications other than the original.

To Dr. D. R. Webster and Dr. D. W. MacKenzie I wish to express my gratitude for their interest, advice and encouragement during the course of these studies and in the preparation of this thesis. I am also indebted to Dr. R. H. More and Dr. D. L. McRae for assistance in the interpretation of the histological and radiological materials respectively.

The tissue sections were prepared by Mr. Hans Torunski and the photographs by Mr. John Isaacs.

To all the members of the Department of Experimental Surgery I express my sincere thanks for their cheerful cooperation and assistance, without which the pursuit of these studies would have been most difficult.

R. H. G.

CHAPTER I

INTRODUCTION

History of Pulmonary Surgery:

From very humble beginnings pulmonary surgery has developed to reach its present status. Fifty years ago the pleural cavity was opened only by the most courageous surgeons. Today the surgeon enters the pleural cavity and examines the contents with no more fear of dire results than he faces when he explores an abdomen.

The development of this field of surgery has been based upon the contributions of many men working both in the laboratory, autopsy room and operating theatre. The numerous problems, considered insurmountable by many prominent surgeons of the last decade of the nineteenth century, have been solved by the persistence of those who refused to accept defeat. To them we owe a great debt. So that others may become familiar with the names of some of those who contributed so much to the development of this field of lung surgery in particular, and thoracic surgery in general, the following historical data has been collected and recorded.

Pulmonary surgery, so far as is known, had its beginnings with Hippocrates, who stated, "When empyema is treated either by the cautery or incision, if pure white pus flows from the wound, the patients recover; but if mixed with blood, slimy and fetid, they die" (42). According to Adams (1), the ancients applied this term 'empyema' not only to a collection of pus between the thoracic cage and the lung but also to a cavity within the lung. This is, therefore, the first record of a scientific, surgical approach to the treatment and cure of a pulmonary disease.

Unfortunately, with the termination of this great period in history, these teachings disappeared for many centuries. Not until 1499 was there any further record of surgery being performed upon the lung. At this time, Rolandus (75) reported the following case.

'Called to a citizen of Bologna, on the sixth day after his wound, I found a portion of his lung issued between two ribs; the afflux of spirits and humors had determined such a swelling to the part that it was not possible to reduce it. The compression exercised by the ribs retained its nutriment from it, and it was so mortified that worms had developed in it. They brought together the most skillful chirurgeons of Bologna who, judging the death of the patient to be inevitable, had abandoned him. But I, yielding to his prayers and to those of his parents and friends, and having obtained the leave of the Bishop, the master and the man himself, I yielded to the solicitations of about thirty of my pupils, and made an incision through the skin, the breadth of my little fingernail away from the wound, all round it. Then, with a cutting instrument, I removed all the portion of the lung level with my incision. The wound resulting from this resection was closed by the blood issuing from my incision, and was dressed frequently with red powder and other adjuvants. By the grace of God it cicatrized and recovery took place. It is true that one had to wait long for it. The patient, with his master, Rolandini, has since then made the voyage to Jerusalem, and has returned in good health. If you ask me what I should have done in this case if I had been called to it at once, I answer that I should have dilated the wound with a small piece of wood, keeping the lung warm with a cock or a fowl split down the back, and should have reduced it, and kept the wound open till the portion of the lung was wholly mortified. If you should still question me, to know how this man can live without his lung, I answer that the part remaining within the chest profits by the nutriment destined for the whole lung, and so is developed, and that nature has been able to creat supplementary parts in it, which is an easy thing in an organ which is soft and near the warmth of the heart'.

Thus, in 1499, there is recorded the first successful resection of a portion of lung, which in this case was for the cure of a traumatic pulmonary hernia.

No further mention is made in the literature of surgery being performed upon the lung until 1584, when Schenk (78) reintroduced the Hippocratic method of treating empyema and lung abscess. This was not, however, generally accepted until 1664 when Willis (93) employed it fairly extensively and convinced others of its value. Unfortunately some very unpleasant results must have been encountered, particularly when the surgeons of that day were unaware of the nature of abscesses. Many a tuberculous cavity must have been drained with tragic results. However, in 1670, Bligny (13) actually reported a case of 'phthisis' cured by the accidental puncture of a pulmonary cavity during a sword fight. The surgical drainage of pulmonary abscesses and empyemata became the treatment of choice with further reports of cases by Purmann (66) in 1692, Baglivi (5) in 1699, Barry (6) in 1726, Sharpe (82) in 1769 and others.

There was, however, no further record of lung tissue being resected from the time of Rolandus' publication until 1674, when Tulpins (88) reported successfully resecting a protruding gangrenous pulmonary hernia. This procedure was immediately accepted for the management of such conditions and Couvy (20) in the latter years of the 19th century collected 14 cases of which twelve survived the operation and were apparently cured.

In a strict sense these cases cannot actually be included under the heading of 'pneumectomy' as they did not involve the difficulties in technique nor the dangers of intrathoracic surgery. A case of deliberate thoracotomy and pneumectomy was finally reported in 1861 by Péan (64). While resecting a tumour involving the third, fourth and fifth ribs, he opened into the pleural cavity and found that the tumour extended into the underlying lung. He therefore sutured the visceral and parietal pleurae together and with the Paquelin cautery excised the involved lung.

There was a frightful mortality rate associated with this field of surgery. A fatal infection almost invariably ensued. Thus Lister's tremendous contributions in antiseptic surgery beginning with his publication in 1865 caused a reconsideration of the whole field of surgery and in particular, thoracic surgery. Within a few years there was less hesitation in operating upon the lung and hence reports of such operations became more frequent.

At about this time reports of animal experiments on the possibilities of safely resecting various quantities of lung tissue began to appear. In 1881 Gluck (30) (31) published the results of his experiments. He had ligated the root of the lung in dogs and rabbits with only two deaths. Carrying his work further, he resected one lung from each of six dogs and fourteen rabbits. Only two rabbits survived, the remaining animals dying within seven to ten days of pleuritis. A few months later Marcus (53) reported one successful pneumonectomy out of five attempts. Schmid (8) in the same year, and without knowledge of Gluck's work, under strict antiseptic technique resected varying portions of lung tissue from eight dogs with three recoveries. In one instant he successfully excised both apices.

Block (14), also in 1881, experienced the same mortality in his experiments. He noted, however, that in the series in which he employed an intercostal incision rather than an approach through a resected rib, he encountered a slightly higher incidence of success. Despite these results Block was so convinced that the operation of lobectomy was feasible and that the dangers of exploration minimal, that he persuaded a relative, whom he thought suffered from tuberculosis to undergo operation. The lobe he resected was unfortunately free from disease and the patient died from the operation. Thus to avoid all the unpleasant consequences he took his own life (89).

The reports of these investigations were discouraging to clinical surgeons but with the publications of Biondi (10) (11) in 1882 to 1884 there was a surge of optimism. He excised the right lung from twenty-three healthy animals with twelve recoveries and the left from thirty-four with eighteen recoveries. Furthermore he resected both upper lobes in three animals and the middle lobe in one without a death. In other experiments he artificially infected some animals with tubercle bacilli and reported that although all control animals died of the infection, a timely resection of the apex of the lung saved many.

Another encouraging report came from Kharkov in 1887. There Zakharevitch (95) in thirteen operations upon nine rabbits resected varying amounts of lung tissue. Only two died from the operation and both of these immediately upon opening the chest. In eleven similar experiments upon seven dogs, he had only three operative deaths, two immediately upon opening the thoracic cavity and one ten days postoperatively from infection. He also dissected cadavers with a view to finding the best surgical approach to the lung root and the optimum place to establish drainage. From his studies, he concluded that 'a minimal respiratory area compatible with life and health amounts to two pulmonary lobes'. Furthermore, 'both experiments on animals, and already published cases of surgical treatment of pulmonary cavities in man completely justify a more active operative interference in various regions of the pulmonary tissue'.

From the clinical side the reports were not so optimistic. Weinlechner (90) in 1882, had a fatal result when, upon resecting three ribs for malignant disease, he excised two metastases from the underlying lung. Kronlein (46), in 1884, lost two tuberculosis patients upon whom he attempted to resect the diseased area in the lung. Ruggi (76) in two similar cases had two similar outcomes. In 1887, however, Sedillot (81) and in 1888, Miller (55) each successfully excised a portion of involved lung tissue beneath a chest wall tumour. Finally Tuffier (87), in 1891, reported successfully resecting a tuberculous nodule from the apex of the lung in a patient.

Many other attempts to excise diseased lung tissue in man were subsequently reported, but the hope that was born from the results of Biondi's and Zakharevitch's studies was not realized. Willard (93) from his personal experiences, as well as from a study of the literature, concluded that it was only safe to enter the lung if parietal and visceral pleurae were strongly adherent. In 1896, Paget (63), in reference to resection as a method of treatment for pulmonary tuberculosis, stated that 'the indications for the operation are so doubtful, the advantages of it so uncertain, that at present there is no clear reason why the surgeon should undertake it'. Two years later at the Annual Meeting of the American Medical Association, Murphy (58) completely summarized the status of thoracic surgery and reported that 'while the operation of removal of a complete lobe of a lung has been successfully performed the number of deaths following pneumectomy has been so large that the operation has been abandoned'. In addition, he said that 'while occasional success in partial resection may be achieved, it can never become a practical method for the treatment of tuberculosis'.

Thus at the turn of the century the future of pulmonary surgery was not promising. The mortality rate of such operations was prohibitive. What were the causes? They were many. Frequently death occurred as soon as the chest was opened and the lung collapsed, or else shortly thereafter from shock. Even if the operation were successful, in the ensuing days death occurred as a result of infection with or without pneumothorax from a reopening of the bronchial stump. Death from tension pneumothorax as a result of a broncho-pleural fistula was not uncommon, or from massive hemothorax, following hemorrhage from a pulmonary vessel in the hilar stump. As is generally the case in a new procedure, the selection of patients for such surgery was poor. The introduction of Roentgenography, towards the end of the last century was of great importance as an aid to selection of cases, and the choice of the appropriate surgical approach. The value of this discovery and the subsequent development of it, as regard to pulmonary disease, cannot be underestimated.

Another great obstacle to further progress in both the experimental and clinical fields was the inability to maintain respiration while the chest was open. Because of this, time could not be permitted for a careful and safe surgical technique. It is true that for a number of years physiologists had been employing artificial respiration by means of an intratracheal tube and bellows in their animal experiments, but surgeons could not be satisfied that such a device could be applied to man. A solution to this difficult problem appeared in 1904. Both Sauerbruch (77) and Brauer (15), working independently, each introduced an apparatus designed so that anaesthesia could be administered and artificial respiration maintained while the thorax was open. The former designed what he called 'a negative pressure chamber'. In this chamber were the surgeon's and all but the patient's head, which extruded through an air-tight collar into the room outside. By alternately increasing and decreasing the negative pressure within this chamber the patient's lungs could be made to inflate and deflate during open thoracotomy, while at the same time the anaesthetist could be administering the anaesthetic in the adjoining room. It had obvious disadvantages so far as the surgeons were concerned who were confined in such a closed space and exposed to the alternating pressures. Brauer's invention, on the other hand, was somewhat more attractive. It was a 'positive pressure apparatus' and consisted essentially of a box in which the patient's head and the anaesthetist's hands, holding the anaesthetic, were sealed. By increasing and decreasing the pressure of the air in this box the lungs could be made to respire. It too, had some obvious disadvantages. Arguments arose as to which was the safer equipment and to combine some of the best features of each, Meyer (54) with the help of his brother, an engineer, devised an ingenious combination of the two. This he called a 'low pressure apparatus'. All three were very cumbersome but they did solve one of the major problems of intrathoracic surgery, and from these rather crude beginnings stems the present day methods of maintaining respiration during open thoracotomy. Their discoveries also served as a stimulus to further experimental and clinical studies, for now it was possible to enter the thoracic cavity and operate at leisure upon the lung.

There was renewed vigour in the laboratories. Investigations were embarked upon with a view to discovering a safe surgical technique for the excision of various quantities of lung tissue. The most difficult problem in this matter was the development of a secure closure of the bronchial stump. This is still a challenging problem, for reopening of the bronchial stump is one of the most common and serious complications in pulmonary resection today. Needless to say, up to the present, the investigations of this have been very extensive.

As it was now possible to totally excise one lung or various quantities of lung tissue with every hope of a successful outcome, attention became focussed upon the affects of such loss upon the animal. Hellin (38) in 1906, Friedrich (26) in 1912, and Kawamura (44) in 1914, and others, described the various intrathoracic anatomical readjustments in different animals following resection of one lung. They, as well as Möllgaard (56) and Möllgaard and Rovsing (57), in 1909 and 1910, carried out histological studies on the remaining, greatly enlarged lung, to determine what happened to it when it was exposed to the total respiratory and circulatory load. Kawamura (44), however, working in Germany in 1914, published the most comprehensive study of this nature. He also attempted to correlate the laboratory findings with available autopsy material. The problem as to what happens to this lung following pneumonectomy has been investigated from various approaches over the years but still there is no unanimity of opinion as to its fate.

From a physiological point of view, as early as 1876 Lichtheim (48) had carried out investigations on the effects of occlusion of one main pulmonary artery as related to pulmonary embolism, and Welch (91) in 1878, Tigerstedt (86) in 1903, and others, extended these studies. They were applicable in part to the effects of pneumonectomy but from 1904 date many direct studies of the physiological consequences attendant upon the total excision of one lung.

All these investigations, both anatomical and physiological, played a most important role in the development of the field of thoracic surgery, by the fact that they gave to the clinical surgeons an appreciation of the dangers involved in resection of lung tissue as well as encouragement as to the end-results of such operations.

Prior to Sauerbruch's and Brauer's work, there were occasional reports of successes and failures of attempts by clinical surgeons to excise diseased lung tissue. The failures exceeded the successes. However, in 1901, Heidenhain (37) succeeded in excising a large portion of a bronchiectatic lower lobe in a patient. Soon after 1904 the reports of successes became more numerous. Stretton (83) in 1906, succeeded in excising a tuberculous right upper lobe. Korte (45) and Robinson (73), in 1911, reported the successful resection of a bronchiectatic right lower lobe and a chronic bronchopneumonic left lower lobe respectively. Kummell (47), in 1911, attempted the total excision of a carcinomatous lung, but unfortunately his patient died on the sixth postoperative day from edema of the remaining lung. There was much to be desired in the surgical management of these cases, but these successes were very encouraging.

In the subsequent years many of the factors which contributed to the high mortality rate were worked out in both operating and autopsy rooms and the laboratory.

Numerous were those who made contributions in advancing further this particular field of surgery. The operation of lobectomy gradually became accepted as the procedure of choice for the treatment of several pulmonary conditions. The operation of pneumonectomy, however, was not performed again until 1931 when Nissen (60) and Haight (35) each successfully removed an entire lung for the cure of bronchiectasis. In these instances both ligated the hilus and permitted the lung to slough out. The great triumph came in April 1933, when Graham and Singer (33) successfully excised, in one stage, a lung for the cure of bronchiogenic carcinoma. Later in the same year Rienhoff and Broyles (71) performed two similar, successful operations. Since then this procedure has found a definite place in the surgeon's armamentarium for the treatment of certain pulmonary diseases.

Pulmonary tuberculosis, on the other hand, seemed to be a formidable condition in which resection had little place. Murphy (58) in 1898, had expressed the opinion of almost all surgeons of that period when he said that 'while occasional success in partial resection may be achieved, it can never become a practical method for the treatment of tuberculosis.' Murphy's pessimistic prediction was dispelled for good with reports published from 1935 on. In this year

Freedlander (25) reported the successful resection of a tuberculous lobe. Those taking part in the discussion of his paper commented upon their experiences admitting successes and failures, and suggesting that there may be a place for resection in the treatment of pulmonary tuberculosis. Both lobectomy and pneumonectomy took a definite place in the management of this condition in 1939, when Jones and Dolley (43) reported two cases of pneumonectomy and two of lobectomy resulting in the successful control of the disease in each instant.

The development of surgical techniques has played a considerable role in the advancement of this field of surgery. However there have been many other factors which have played an essential part in making the operation of resection a warranted procedure for many pulmonary diseases. The advancements in the prevention and treatment of surgical shock, have played an invaluable role; so also advancements in the pre- and postoperative care, particularly in reference to nutritional state; so also advancements in anaesthesiology; and finally, so also advancements in the control and treatment of infections by chemotherapeutic and antibiotic agents. All these important developments have enhanced the progress of pulmonary surgery by not only extending the range of conditions amenable to such surgery, but also by steadily reducing the mortality rate from operation to reasonable levels. For example, the operative mortality rate from pneumonectomy in bronchiogenic carcinoma in most hands is only about 16% (61) and in pulmonary tuberculosis, since the introduction of streptomycin, the mortality rate from resection has dropped from about 25% to about 4.5% (59).

Thus has the operation of pneumonectomy been developed and advanced. The fifty years which have passed since Murphy's pessimistic pronouncements have seen pulmonary surgery progress beyond the fondest hopes of surgeons of the nineteenth century. There are still many problems to be solved and new discoveries to be made.

Object of Present Investigations:

As a particular interest of the author lies in the field of thoracic surgery, it seemed advantageous for him to carry out investigations, the pursuit of which would lead to an understanding of many of the problems confronting thoracic surgeons today. At the same time, such studies would necessitate a thorough review of the literature and the actual experimentation would permit the development of a surgical technique in lung resection. It has been his aim to emerge from his studies with an extensive knowledge of present-day problems. Thus was this rather brief history of the operation of pneumonectomy recorded.

In the historical review it was observed that, as the operation of lung resection was being evolved through the years, many problems were encountered, both from the technical and anatomical and physiological points of view. There is still controversy concerning certain subjects. It is therefore the object of these present investigations to reexamine some of the various problems in the light of our experimental studies. By this means, it is hoped that many of the controversial issues will be somewhat clarified.

In the first instant, the second chapter is devoted to the bronchial stump. There is still considerable controversy as to the correct method of occluding the sectioned bronchus. Postoperative broncho-pleural fistula is still all too frequently a complication of lung resection. An understanding of the mechanism of bronchial healing permits a more rational approach to the problem. This we shall present and shall reexamine the previous studies in the light of our investigations. Thus it should be possible to draw conclusions as to the best method of closing a bronchus so that the incidence of postoperative broncho-pleural fistula will be minimal.

The problem which precipitated the various ancillary studies was what happens to the remaining lung after pneumonectomy. In approaching this, it was necessary first to know the anatomical readjustment of thoracic organs following the excision of one lung. The third chapter is devoted to this subject. The following, and last chapter, tackles the problem of the fate of the remaining lung from an anatomical and histological point of view. Here, the controversy arises as to whether or not the remaining lung becomes simply over-distended, emphysematous, hypertrophied or hyperplastic. Many contend that the lung becomes over-distended and subsequently emphysematous, in the true sense. They therefore recommend that measures be taken to prevent this over-distension. This generally means an extensive thoracoplasty. If, on the other hand, the remaining lung undergoes hypertrophy or hyperplasia, then such a deforming procedure becomes unnecessary and may even be harmful in that it may reduce pulmonary function. Here we shall review all the previous investigations and to them add our own.

In the discussion of this subject we shall attempt to correlate some of the physiological and functional studies which have been reported. Thus, from this overall picture, it is hoped to arrive at some definite conclusions which may lead to a clarification of this controversial subject.

General Consideration of Materials:

The exact age of the animals is important in the investigations of the fate of the remaining lung. It has been reported by many investigators that the effect of pneumonectomy upon the remaining lung in growing animals differs entirely from that in the mature. For this reason we were anxious that all our animals be full grown. Because it was impossible to obtain animals of known age, it was necessary to select only those which, so far as it was possible to determine, were full grown. This was accomplished by examination, which in some doubtful instances involved the use of the x-ray.

Furthermore, at one time, due to a shortage of dogs, rabbits were considered and pneumonectomies performed upon several. Shortly thereafter, the literature revealed that animals of the rodent family have a growth response differing entirely from that of carnivors, including man. Therefore these were discarded in the study of the remaining lung and used only in the investigations of the bronchial stump and intrathoracic readjustments. Because cats could be obtained with relative ease, it was decided to use them in the experiments as well as any dogs which might become available from time to time.

Some explanation is necessary concerning the number of cats actually employed in these studies. It was hoped to have at least twelve survive for over one year postoperatively. The total number which were subjected to operation was twenty-two. The number which survived for over one year was only seven. Five died of known causes, three directly as result of the anaesthetic. One animal, upon being found dead, was put in the incinerator by the animal attendant against specific instructions to save all dead animals until they had been examined. The nine remaining, all alive and apparently healthy three weeks to one month postoperatively, disappeared during a period when the author was on vacation and when the laboratory was in a state of turmoil in preparation for moving to new quarters. The fate of these is entirely unknown.

A small problem arose in the selection of anaesthetic to be used. When nembutal was tried in the rabbits a high mortality from the agent was experienced. It was found necessary, in order to obtain relaxation of the larynx for intubation, to employ a very heavy dosage of this substance. As a result, only two out of six animals recovered from the anaesthetic. A similar situation arose when it was employed in the cats. Two cats died before the operation was even started. Three others died within ten days of pneumonia, which was felt to be a direct consequence of the prolonged postoperative period of unconsciousness. This anaesthetic agent was therefore discarded and a technique devised for the administration of continuous ether. This proved to be a very satisfactory anaesthetic and no deaths attributable to it occurred in the seventeen instances in which it was employed.

Intravenous nembutal, on the other hand, proved to be an entirely satisfactory anaesthetic without complications when used in the operations upon the dogs.

No special postoperative care was given to any of the animals. Generally, as soon as they recovered from the effects of the anaesthetic, they were up and moving about and within a few days were apparently completely recovered.

CHAPTER II

THE BRONCHIAL STUMP

Introduction:

One of the major technical problems in lung resection still confronting surgeons, is that of accomplishing an air-tight, permanent closure of the sectioned bronchus. It is accepted that the bronchial cartilages may become necrotic as a result of a relatively mild trauma and that their regenerative powers are poor. Furthermore, the anatomical structure of the bronchus is such that it is designed to remain patent, consequently an accurate approximation of the walls without trauma to the cartilages and stress upon sutures is technically difficult, if not impossible. Thus today, one of the most frequent and most serious complications attendant upon lung resection is the reopening of the stump of the bronchus, occurring at any time up to three weeks postoperatively. The sequelae are several. A tension pneumothorax may rapidly ensue with death from respiratory failure. A fulminating empyema may develop associated with a pneumothorax. Should a patient survive these complications, due to a timely thoracotomy, a broncho-pleural-cutaneous fistula may persist for months or even years. In pulmonary surgery upon animals, on the other hand, the opening of the bronchial stump is invariably fatal, death being either due to the pneumothorax and/or fulminating infection.

The seriousness with which reopening of a bronchial stump is viewed, is reflected in the intensive studies carried out in the laboratory to discover a reliable surgical technique of bronchial closure. It is not the intention of the author to review completely the voluminous literature on this subject, because the majority of articles merely describe various methods recommended to ensure closure of the sectioned bronchus. The fact that there are such numerous papers indicates that there is no solitary, completely reliable technique. It is therefore important to approach the problem through fundamental concepts, namely the factors involved in, and the mechanism of, healing. Some of the more important contributions in the literature will consequently be considered.

Historical:

In the earliest experiments on surgical excision of the lung ligature en masse of the hilus was performed with section distal to the ligature. The results were discouraging. The animals died either from slipping of the ligature with massive hemorrhage, necrosis with hemorrhage or later from broncho-pleural fistula and its associated complications.

Tiegel and Mitt (85), in 1907, realized that this was a very primitive technique so they recommended that a temporary, loose ligature be placed about the whole hilus to control hemorrhage, followed by a separate ligation, with silk, of the vessels and cauterization and ligation of the bronchus. In the following year Friedrich (27) advised a similar technique but for the bronchus suggested curettage of the mucosa and ligation so as to bring into apposition the raw surfaces.

Up to this time little attention had been given to the choice of suture material. Most investigators soon began to recognize that the incidence of complications was less when silk was employed rather than absorbable materials. Danielson (22) expressed this when he concluded that it was quite possible to obtain a permanent closure of the bronchus using silk. Thus it became the suture material of choice.

In America, Halsted (36) suggested treating the bronchial stump by bisection and removal of the mucosa then approximation of the flattened halves with through and through silk sutures together with a series placed along the edges. This method was specifically designed to obviate the mechanical strain placed upon sutures by the bronchial cartilages and to obtain permanent closure through healing from within the bronchus. On the other hand, Meyer (54) proposed treating the bronchial stump very much as one treated an appendix, namely by brushing, ligating and inverting the end by means of sutures in the peribronchial tissues. Both these methods showed improvements in the results of resection over the mass ligation technique in which, for example, Robinson and Sauerbruch (74) had lost thirty-four out of thirty-eight dogs and Schlesinger (79) twelve out of seventeen. However they were not the answer to the problem.

Some conception of the mechanism of healing began to appear in 1910 when Tiegel (84) observed that bronchial wounds healed best when the sutures were placed in the peribronchial tissues. The following year Quinby and Morse (67) reported an investigation of all the various methods of treating the bronchial stump and concluded that healing depended upon the peribronchial tissues and that the method recommended by Meyer (54), so far, gave the most satisfactory results.

Broncho-pleural fistulas still occurred with undue frequency so further attempts were therefore made to discover a really reliable technique. Garrè and Quincke (28) advocated sewing a leaf of lung tissue over the ligated bronchial stump but this had the obvious disadvantage of necessitating amputation through lung tissue thereby leaving within the chest a mass which, in man at least, would harbour infection. Henschen (39) suggested introducing a plug of fascia into the lumen of the bronchus and suturing the free end over it. Giertz (29) modified this by suturing a small fascial transplant over the end after first occluding the cut bronchus with silk mattress sutured.

Kawamura (44) made a study of the various methods of closure and came to the conclusion that although the method advocated by Meyer (54) was good, it could not be employed in all instances. From his experiments he concluded that the most satisfactory method for all cases was one consisting of amputation of the hilus between two soft rubber clamps and isolation and ligation of vessels and bronchi separately followed by a precise closure of the hilar incision with a continuous suture. With this technique he had only two deaths from broncho-pleural fistulas in twenty-three pneumonectomized dogs.

The whole subject was reviewed again in 1920 by Heuer and Dunn (40). In their investigations they evaluated the various procedures and devised several new ones. Of twenty-three dogs operated upon they lost only two from broncho-pleural fistulas, one of these failures being intentional. They felt, from their review of the literature, that the frequency of broncho-pleural fistula associated with the mass ligation technique was conclusive evidence that this method was inadequate. Admitting that they gave no one method an extensive trial, they concluded that, at least in dogs, every method so far recommended, excepting mass ligation, was technically feasible and if performed carefully, even the simplest was adequate to ensure satisfactory closure. Certainly their results would seem to bear this out.

From 1920 to the present there have been many reports in the literature of various surgical techniques for bronchial closure designed to lessen the complication rate but none have had anything definite to offer and have therefore not gained acceptance.

A study of the literature brings forth certain facts of importance. Firstly, the results of mass ligation are invariably poor in comparison to individual ligation. Secondly, the use of absorbable suture material results in a higher incidence of broncho-pleural fistula than the use of non-absorbable material. Thirdly, traumatizing the bronchus by crushing prior to ligation, in many instances, seemed to give a higher incidence of complications. Fourthly, techniques employing considerable dissection of the hilar structures did not seem to give as satisfactory results as simpler procedure. Fifthly, the peribronchial tissues appeared to play an important role in obtaining permanent closure of the bronchial stump. Finally, it was demonstrated by Heuer and Dunn (40) that healing of the stump of the bronchus occurred, for the most part, through the formation from the peribronchial tissues of a plug or cap of fibrous tissue over the sectioned end. This important observation has since been confirmed by Bettman (8), Bettman, James, Tannenbaum and Slobe (9), and Adams, Van Allen and Livingstone (4).

None of the studies gave all the reasons for the failures. Longacre (49) in 1935, attempted to present these. He stated that all the difficulties in obtaining permanent closure of the bronchial stump could be explained on the basis of the anatomical structure of this organ. The very shape and elasticity of the cartilaginous rings, he stated, by continually straining to separate the apposed walls, tended to promote fistula formation. Furthermore, the cartilaginous rings are prone to degenerate, if traumatized, due to interference with their normal, meager blood supply. The blood supply, as a whole, to the bronchus is poor for the bronchial arteries are almost the sole supply. In addition these bronchial arteries, he said, play a most important part in the actual mechanism of healing because they also supply the peribronchial tissues upon which permanent closure of the sectioned bronchus depends, as Heuer and Dunn (40) and others (8), (9), (4), had demonstrated. Therefore Longacre concluded that any interference with this already scanty blood supply would lead to either actual necrosis of the bronchus or to delay of the peribronchial tissues in participating in the healing process. Either could lead to broncho-pleural fistula formation. He concluded that healing of the stump must of necessity be slow and therefore any process which might further delay it, such as infection, must obviously increase the likelihood of fistula formation. Longacre furthermore proved what had already been the experience of others, that absorbable sutures should never be employed. Of twelve dogs in which he employed twenty-day chromic catgut to close the bronchus nine developed fistulas whereas of eighteen dogs in which he employed silk only one developed a fistula. The histological examinations of the specimens revealed a marked inflammatory reaction about the catgut whereas there was only slight reaction about the silk.

This inflammatory reaction about catgut he felt delayed healing.

It would appear from a review of the literature then, that there is now no great problem and that with careful handling of the bronchial stump broncho-pleural fistulas should rarely occur. Clinically they occur all too frequently. Thus, as the main subject of this thesis necessitated the performance of many pneumonectomies, it was felt that a study of the bronchial stump was warranted, if for nothing else, to stress and confirm the work of Longacre (49). Consequently, in performing the pneumonectomies, several different techniques were employed in closing the bronchial stump, but at all times the fundamentals of healing, which he had outlined, were observed.

Materials:

The bronchial stumps of twelve pneumonectomized cats, nine pneumonectomized dogs and two pneumonectomized rabbits were studied grossly and microscopically. Four specimens were less than ten days postoperative, three between eleven and twenty days, and two between twenty-one days and one month. The remainder were from animals which had either died or had been sacrificed up to almost eighteen months after operation and in which the healing process could be expected to be complete (Fig. I).

Postoperative Periods	Cats	Dogs	Rabbits	Total
0 - 10 Days	3	1	0	4
11 - 20 Days	1	1	0	2
21 Days - 1 Month	1	1	1	3
1 Month - 3 Months	0	4	0	4
3 Months- 6 Months	0	1	1	2
6 Months and over	7	1	0	8
			Grand Total	23

Figure I

Table indicating the number of animals and periods at which studies were made.

Methods:

Pneumonectomy, either right or left-sided, was performed under nembutal anaesthesia in the case of the dogs, and, for the most part, inhalation ether in the case of the cats and rabbits. All animals were intubated and artificial respiration maintained by means of a positive pressure pump, while the pleural cavity was open. Using strict aseptic technique, the lung was approached through an intercostal incision, usually in the sixth or seventh interspace. Various surgical techniques were employed in dealing with the hilar structures. In all the cats and rabbits the lung was removed in the same manner. The pulmonary ligament was freed and a solitary, heavy silk ligature placed about the hilus and tied as closely as possible to the mediastinum. It was tied just tightly enough to occlude both vessels and bronchus. The hilar structures were then transected with the scalpel about two to three millimeters distal to the ligature and the lung removed.

The chest incision was then closed in the following manner. The adjacent ribs were approximated by two or three pericostal sutures of heavy silk, the muscle layers were approximated by continuous sutures of fine cotton and the skin incision was closed with a continuous suture of number 00, plain catgut.

The operation performed upon dogs was in most respects similar to that upon cats, and differed mainly in regards to the handling of the hilus. In one animal the lung was excised using the mass ligation method. In all others an individual dissection and ligation technique was carried out on the hilar structures. In all the dogs the stump remaining was either buried in the mediastinum or covered with a flap of mediastinal pleura, sutured in position by a fine, continuous silk or cotton suture.

In these dogs the bronchial stump was closed in several different ways. In one instant heavy interrupted silk sutures were placed over the end approximating the flaccid posterior portion with the anterior rigid arch. Air-tight closure was not obtained due to holes created by the large needles and the heavy sutures thus a few, fine, vertical mattress sutures had to be placed proximally and this manipulation proved successful. In another animal the bronchus was occluded by a proximal and distal row of vertical mattress sutures of medium silk and again the flaccid portion approximated to the anterior arch. In three other animals a similar technique was employed but using fine silk. In another three animals the bronchial stump was closed by interrupted, over-end sutures of medium, fine silk, the flaccid posterior wall again being approximated to the anterior arch.

In the dogs the approach to the lung and closure of the incision were essentially the same as in the cats and rabbits, excepting that interrupted sutures of fine cotton were employed in closing the muscle layers and the skin. Where the individual dissection and ligation technique was employed, particular care was practiced so as to disrupt, as little as possible, the peribronchial tissues. The bronchial arteries were thus disturbed to a minimal extent and were sectioned along with the bronchus. Therefore it was hoped that the blood supply to the stump would be preserved right up to the point of section. The bronchial arteries being very small in these animals it was rarely necessary to ligate them to control bleeding. In every instant in which the individual ligation technique was employed it was noted that the stump retracted deeply into the mediastinum.

The animals when they died or were sacrificed were autopsied in the manner described in Chapter III. Sections for microscopical study following fixation, as described in Chapter IV, were taken from the stump parallel to the long axis so as to include anterior and posterior walls as well as the sectioned end. These were stained with hematoxylin and eosin, Masson's trichrome, and Wiegert's elastic tissue stains.

Results:

A study of the specimens from animals which died within ten days postoperatively (cats #79, #25 and #85 and dog #35) was most interesting. In the dog, which died three days postoperatively, the chest and hilus showed grossly little change from the appearance at completion of operation. In the cats, however, there was a blood-clot of varying firmness adherent to the raw surface of the stump. On testing all specimens for evidence of a leak, during the inflation with formalin of the remaining lung, none was found. Examination after fixation revealed the sutures to be essentially in the position in which they were placed at operation. On microscopical study of the sections taken, a heavy hemorrhagic infiltration extended into the loose peribronchial connective tissue about the stump and over the end. In this there was considerable fibrin deposition. In the later specimens of this period early fibroblastic proliferation in the peribronchial area became apparent. In addition there was some proliferative activity of capillaries. There was scant evidence of collagen deposition by the fibroblasts up to ten days postoperatively. The cartilaginous tissue in the region of the ligatures showed beginning necrosis. There was no discernible activity in either the mucosa or submucosa. From these studies it was apparent that up to ten days postoperatively there was little evidence of secure healing of the bronchial stump and all the cellular activity was confined to the peribronchial tissues. Air-tight closure appeared to be entirely dependent upon the sutures.

The two specimens examined in the period between eleven and twenty days postoperatively, one a fourteen day specimen from cat #78 and one a fifteen day specimen from dog #10, revealed grossly much the same picture as the early group except that the 'clot' at the end of the stump was firmer and more strongly adherent (Fig. II). Microscopically in both the fibroblastic and capillary proliferation in the peribronchial tissue was marked (Fig. III). Young fibroblasts and capillaries could be seen extending out into the hemorrhagic infiltration and over the end of the stump. There was a moderate amount of collagen deposition which was more marked in the later specimen. The cartilage in the region of the sutures displayed a greater degree of necrosis than in the first group, and there was beginning foreign

Figure II

Dog #10. Bronchial stump. 12X H. & E. stain

Note: 1. Cap of tissue occluding sectioned end.
2. Approximation of walls at point of ligature.
3. Mucosa bridging across just proximal to point of occlusion.
4. Cyst-like structure created by 'cap' and ligature.

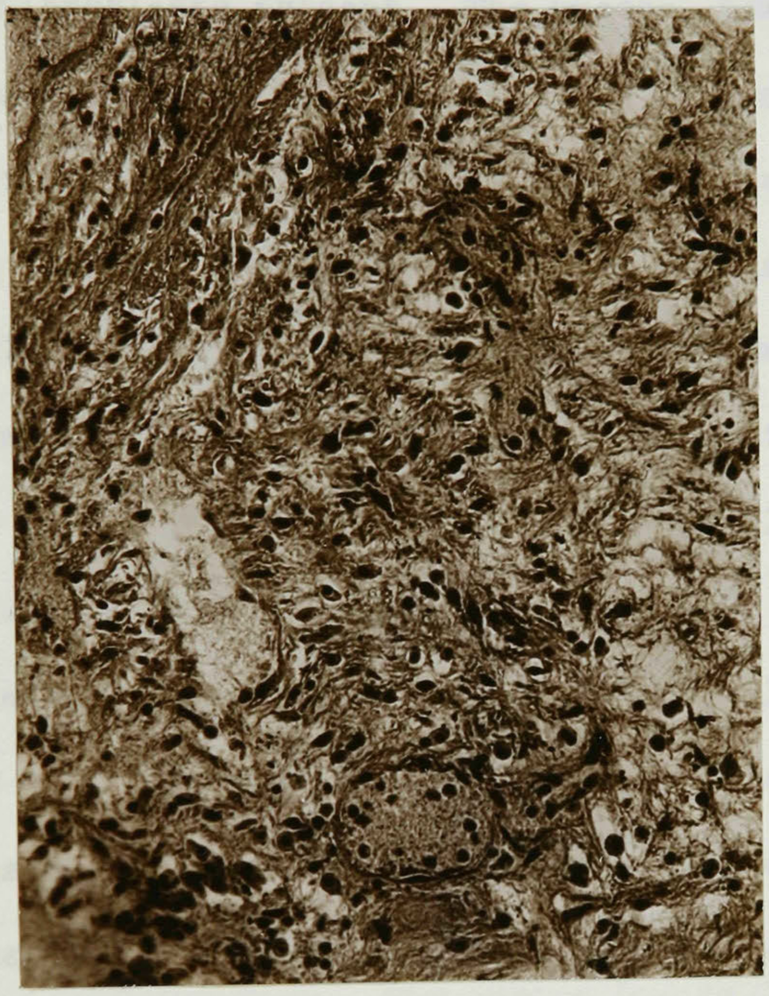


Figure III

Dog #10. Peribronchial tissue of stump near point of section. 240X

Note: Capillary and fibroblastic proliferation with some collagen deposition.

body reaction about the suture material. The submucosa appeared slightly more congested than normal and there were a few young fibroblasts present. The mucosa, however, could be seen compressed between the approximated walls and extending out to the cut end. There was no evidence of fibroblastic activity at this point of compression in the submucosa. The mucosa, in the dog specimen, however, had bridged across at the point of occlusion, so that the stump was lined by a continuous layer of mucosa (Fig. II). The bronchial stump in this animal had been occluded by a proximal and distal layer of mattress sutures, and a small segment of bronchus was thus left flared out at the end. Here, there was fibroblastic and capillary activity in the peribronchial tissue at the point of occlusion and this extended out and covered the flared end of the stump (Fig. II). The mucosa had bridged across internally at the medial end of the point of occlusion and was flattened at the point of compression. Thus distal to the point of occlusion there was a small cystic area, partially lined by mucosa, the distal wall consisting of the granulations covering the end of the stump, the lateral walls essentially normal bronchus and the medial wall the bronchus at the point of ligature (Fig. II).

The specimen from the cat was very similar, only the cyst-like structure was absent. In both the granulations were immature, although abundant, and the healing appeared almost solely confined to the peribronchial tissues. The picture did not suggest firm healing and it would seem that the maintenance of air-tight closure was still largely dependent upon the sutures.

The specimens examined between three weeks and one month postoperatively showed grossly, in two animals, cat #31 and rabbit #67, in both of which the lungs had been removed by means of the mass ligation technique, a firm, greyish-red mass in the region of the hilus and in which the bronchial stump was found to be buried. Microscopically the bronchial stump of both appeared to taper to the point where the ligature was tied. The mucosa had bridged across within and there was a mild fibroblastic activity occurring in the submucosa at this point. However, the submucosal tissue could be seen streaming through between the apposed walls and the cartilage at this point was quite degenerated. There was a dense fibroblastic reaction in the peribronchial area and this extended over the end. Collagen deposition, associated with mature fibrocytes, was in abundance. Healing appeared secure. In the region of the ligature there was considerable foreign body reaction.

The specimen taken from dog #12, which died from distemper twenty-eight days postoperatively, revealed on gross examination, a puckered, injected scar of the mediastinal pleura at the point where the hilar structures originally emerged. On examination of the bisected specimen the stump had a slightly tapered, rounded, ballooned-out end. Microscopically the bronchial walls tapered slightly as the end was approached. The normal bronchial wall ended abruptly and from there on, covering and blocking the end of the stump was a layer of dense fibrous tissue, slightly less than the thickness of the normal bronchus wall. It was lined with essentially normal bronchial mucosa continuous with that of the normal bronchus. This fibrous tissue formed the ballooned-out cap over the end of the stump.

In considering these three specimens, it would seem that in those of the cat and rabbit, the former being twenty-eight and the latter thirty days postoperative, the solitary ligature maintained the stump closed while the fibroblastic reaction of the peribronchial tissues gradually replaced it in function and formed, as well, a cap over the end. The result was a gradually tapered stump. On the other hand, the specimen from the dog was entirely different. Healing took place apparently in the normal manner but sometime before healing was absolutely secure the sutures in all probability cut through and the bronchial walls sprung apart. The cap of fibrous tissue, however, was able to withstand the strain and although ballooned-out and thinned it maintained the stump air-tight. The bronchial epithelium apparently grew out from the sides to line this cap.

The specimens examined between one and three months postoperatively were all from dogs and were essentially similar to that from dog #12, with the exception of dog #15. The gross appearance when the chest was opened at autopsy was not unlike that of dog #12. However when the stump was examined the walls were essentially parallel until the end was reached and here this was bridged across by a dense fibrous cap (Fig. IV). On opening the stump a reddish-grey, friable mass protruded from the cap into the lumen (Fig. IV). Microscopical examination confirmed the gross impression that the cap, for the most part, was comprised of dense, mature fibrous tissue. When the lumen of the stump, however, was approached from without the fibrous tissue of the cap became more vascular and infiltrated with small round cells and occasional polymorphs. Further in the fibroblasts became more immature and budding capillaries appeared. The infiltration of the inflammatory cells became very dense and the tissue more vascular and congested (Fig. V). When the lumen

Figure IV

Dog #15. Bronchial stump. 15X H. & E. stain.

Note: 1. Squared appearance of end.
2. Dense fibrous cap occluding stump.
3. Granulomatous mass extending into lumen.

Figure V

Dog #15. Junction of fibrous cap and granuloma.
240X H. & E. stain.

Note: 1. Dense fibrous tissue of cap.
2. Inflammatory infiltration, capillaries and fibroblasts of granuloma.

was reached there were only fragments of mucosa scattered here and there on the surface of this granulomatous mass.

To explain this lesion, the course of events must have been essentially as in dog #12, excepting that a low grade inflammatory process developed in the cap and persisted up to the time of death. It is to be expected that secretions might tend to puddle in the blind end of the stump, as there is not the action of respiration to maintain good drainage. Thus puddling with attendant infection might be expected.

The specimens examined later than the third post-operative month were taken from seven cats, two dogs and one rabbit. All these animals had been operated upon using the mass ligation technique, excepting one dog in which the individual dissection and ligation technique was employed.

In two of the cats there was a dense fibrous adhesion mooring the stump to the lateral chest wall (Fig. XIV), Otherwise all the cats and the rabbit revealed a gross and microscopical picture essentially similar to the cat and rabbit specimens examined between three weeks and one month postoperatively, the only differences being that the fibrous tissue was mature and the sutures were being broken up by the foreign body reaction (Figs. VI and VII). The one dog specimen was similar to the previous group. The other, taken from dog #20 which was sacrificed almost one and one-half years postoperatively, presented a most unusual lesion of the bronchial stump. In this instant the mass ligation technique had been employed. On gross examination there was a dense fibrous adhesion between the hilar region and the lateral chest wall (Fig. XVI). On opening the stump it was seen to taper rapidly to the point of occlusion. About two to three millimeters distal to this was a round mass approximately two and one-half centimeters in diameter which on section was found to contain a whitish, opaque, gelatinous material (Fig. VIII). The wall of this cystic structure was thin and embedded in a loose fibrous stroma. At the point of occlusion of the stump the fibrous tissue became very dense.

Microscopically the stump was occluded by a dense mass of fibrous tissue covering the end at the point of ligation (Fig. VIII). The submucosal tissue appeared to stream through into this mass between the rings of cartilage (Fig. IX). In addition, immediately beneath the mucosal lining at the point of occlusion the fibrous tissue in the submucosa became continuous with that of the bronchial wall

Figure VI

Cat #91. Bronchial stump. 12X H. & E. stain

Note: 1. Tapered appearance
2. Dense fibrous cap.
3. Fragmented ligature.

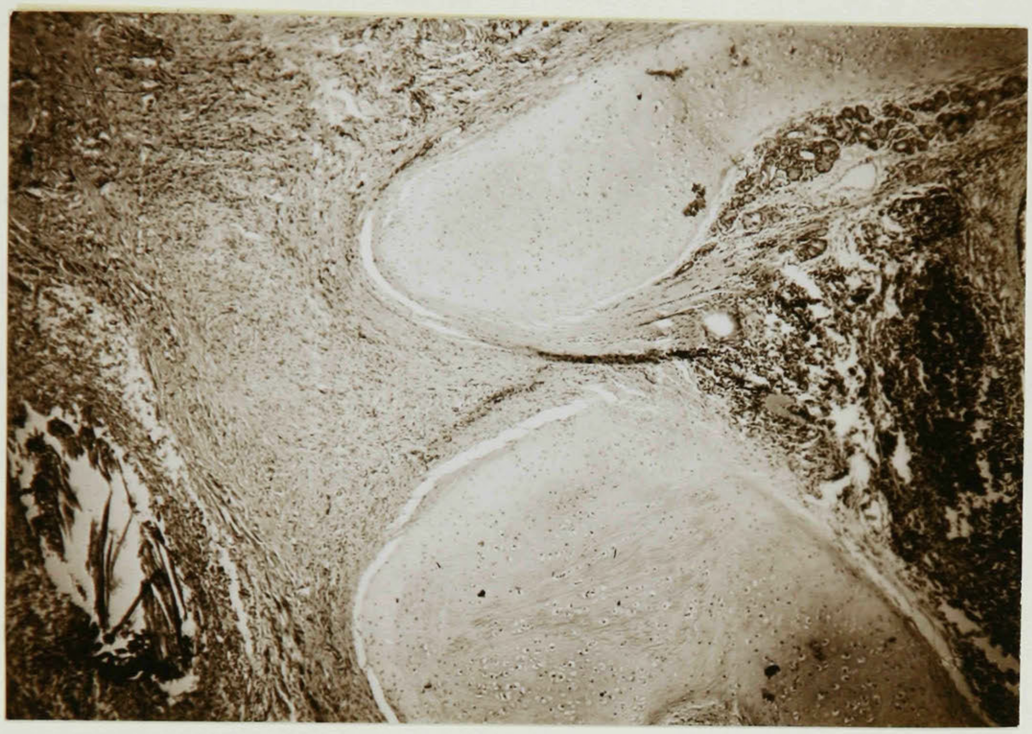


Figure VII

Cat #91. Bronchial stump at point of occlusion. 24X H. & E. stain

Note: 1. Approximation of cartilage.
2. Dense fibrous cap.
3. Foreign body reaction about ligature.

on each side (Fig. IX). The cartilaginous rings disappeared at the point of ligature to reappear fanning out onto the wall of the cyst (Fig. VIII). The remainder of the wall was composed of a thin layer of dense fibrous tissue. The whole of the structure was lined by a low columnar to flattened cuboidal epithelium. In several areas the cells could be seen desquamating into the lumen where they appeared as large, pale-staining vacuolated structures (Fig. X). The remainder of the material filling the cyst, on hematoxylin and eosin staining, consisted of an amorphous pale pink staining mass with occasional darker areas.

To explain this lesion, it would seem that occlusion of the stump took place at the point of ligation through the peribronchial tissues and a lesser extent through the submucosa. Distal to this there was a portion of the stump which survived. The fibroblastic reaction took place in the peribronchial tissues and covered the end of this and the whole became lined by the mucosa extending out from the remnant of the stump. The mucosa secreted in the usual manner and filled and distended this structure resulting in gradual compression of the epithelium and stretching of the walls. The secretions gradually became inspissated, and the result was the picture observed at autopsy. The specimen from dog #10 (Fig. II)

Figure VIII

Dog #20. Bronchial stump. 12X H. & E. stain

Note: 1. Tapered stump with dense fibrous cap occluding.
2. Cyst-like structure distal to point of occlusion. A few fragments of cartilage visible in wall of cyst. Homogeneous mass filling cyst.

Figure IX

Dog #20. Bronchial stump. Point of occlusion.
48X Elastic stain.

Note: 1. Elastic fibers outline submucosa as it streaks through point of ligature.
2. Submucosa has bridged across.

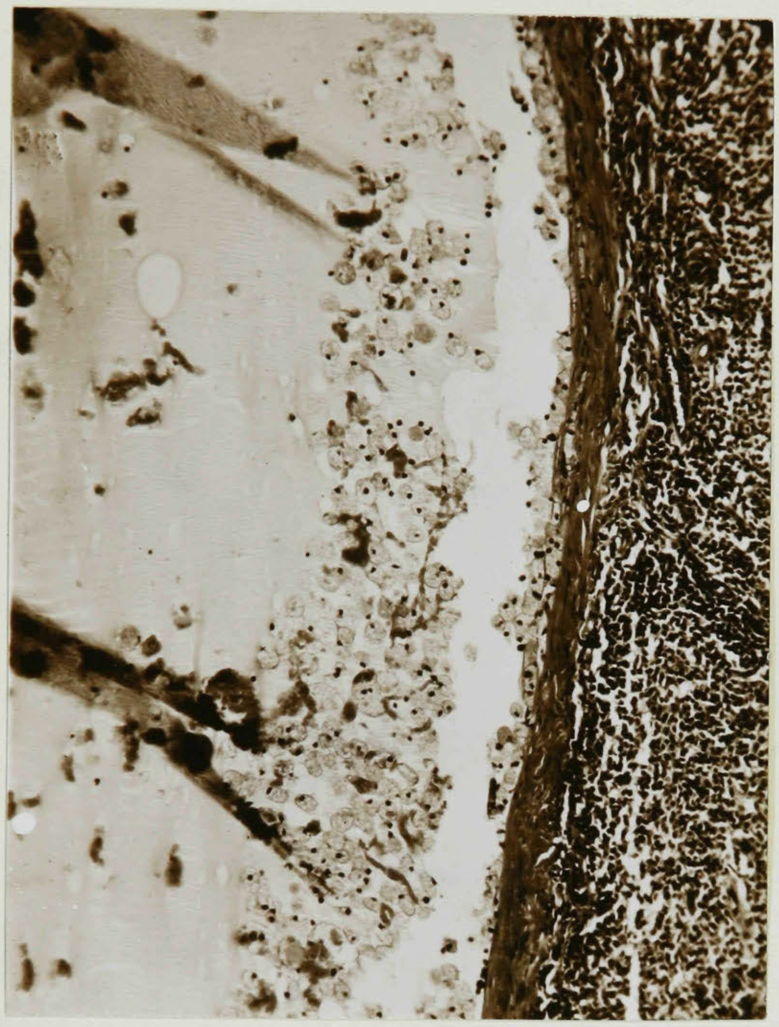


Figure X

Dog #20. Portion of wall of bronchial stump cyst.
240X H. & E. stain.

Note: 1. Thin wall of dense fibrous tissue.
2. Homogeneous material in cyst.
3. Desquamating epithelial cells.

could well be a step in the pathogenesis of this particular lesion.

Discussion:

For the most part, these experiments have confirmed the observations of others (40),(8),(9),(4),(49) that the healing of the sectioned bronchus is from the peribronchial connective tissue through the formation of a fibrous cap over the end. This healing process is slow even in the healthy, normal animal. During the first two weeks post-operatively, in all the animals, the developing cap consists of a hemorrhagic infiltration, with immature fibroblasts and accompanying capillaries gradually replacing it and little, if any, collagenous deposition. It is obvious from these histological sections that such tissue would be unable to withstand, alone, the strain of intrabronchial air pressure and that therefore the air-tight closure depends almost entirely upon the sutures. During this period too, it is noted that at the point of ligature the ensnared cartilage is undergoing necrosis so that the ligatures are tending to cut through. There is generally little reaction in the submucosa but the mucosa, on the other hand, may have bridged across at the point of occlusion thereby sealing the end.

Between the beginning of the third week and the end of the first month after operation the healing process becomes secure and independent of the sutures. The fibroblasts are gradually becoming mature and collagen deposition abundant. The sutures may or may not have either cut through or possibly become disrupted. Should they cut through, then the elastic bronchial walls spring apart so that the end takes on a squared or ballooned-out appearance and air-tight closure becomes entirely dependent upon the fibrous cap (Fig. IV). On the other hand, when an encircling ligature is used, particularly in the smaller animals, and this holds while the fibrous reaction takes place, the stump may take on a tapered appearance (Fig. VI). Considerable foreign body reaction but no acute inflammation is present in the region of the silk ligatures. There is, in all instances, only minimal evidence of fibroblastic reaction in the submucosa.

Later specimens merely demonstrate a further maturation of this healing process in most instances.

In the larger animals, with large, more rigid and elastic bronchi, the tendency is for the ligatures to either cut through or perhaps break. This is probably due to the strain put upon them and the pressure exerted upon the cartilaginous rings by the inherent tendency of the bronchi to maintain patency. Thus, generally the specimens from the dogs in the later periods showed a square-ended or ballooned stump occluded by a cap of dense fibrous tissue. On the other hand, in the smaller animals the bronchial walls are soft and relatively non-resistant to occlusion, so that they can be closed with only minimal strain upon the ligature. Thus these ligatures do not tend to cut through and therefore hold for longer periods during which time the fibroblastic reaction in the peribronchial tissues can gradually take over and replace them in function. Although the silk ligature is eventually destroyed through a foreign body reaction, the bronchial stump maintains the tapered appearance.

These experiments would indicate that any method of closure of the stump of a sectioned bronchus in dogs, cats and rabbits may be employed with assurance of a good result, provided the principles, as stated by Longacre (49) in his paper on the reasons for the failure of bronchial stumps to heal, are observed. In every experiment we carefully avoided excessive dissection of the bronchus so as to maintain the bronchial artery blood supply and the peribronchial connective tissue. In addition we used only silk sutures in or about the bronchus. As proof of the importance of these two factors, we encountered no incidence of broncho-pleural fistula, whereas others, excepting Heuer and Dunn (4) and Longacre (49), had encountered a high one.

The importance of employing a low reacting, non-absorbable suture was demonstrated by Longacre (49) who observed nine fistulas in twelve dogs in which he employed twenty-day catgut to close the bronchus while only one in eighteen dogs in which he used silk alone. The fact that there is marked inflammatory reaction about catgut and only slight reaction about silk, as he demonstrated, is important, for an inflammatory reaction may delay healing which, even under the best conditions, is slow. Furthermore, absorbable sutures in the presence of infection disintegrate at a more rapid rate and would thus be likely to give way before healing becomes secure. Obviously, even when silk is employed as the suture material, the smaller the amount needed to obtain air-tight closure the better.

What would seem to be the preferable method of closing the bronchial stump? Any method might be employed which preserves and disturbs the peribronchial tissues and blood supply to the minimal degree. The mass ligature is quite satisfactory for small animals with soft, relatively non-resistant bronchi. In the larger animals it is undesirable, for, due to the resistance of the bronchi to closure, considerable pressure is necessary and in tying such a ligature there is great danger of cutting through a pulmonary artery or vein. Furthermore, one can expect the ligature to cause necrosis of the bronchial cartilages and eventually cut through, perhaps before healing is secure. Although it might be successful in some cases the experience of others (40) and the early clinical experiences have demonstrated conclusively that this method is unsafe. For obvious reasons too, even in the individual ligation technique, a solitary, encircling ligature on large bronchi is undesirable. Thus the method of closure of these large bronchi should be one in which the least strain possible is exerted upon the ligatures and hence the least pressure upon the cartilages. The anatomical structure of the bronchus would suggest that this is obtained by approximating the flaccid, posterior portion with the rigid, anterior arch. The simpler the method of closure and the less the suture material required, the better. Thus simple, over-end, interrupted, medium to fine silk sutures with approximation of the flaccid posterior portion to the anterior arch would seem to be the method of preference. This results in a minimum of pressure exerted on the cartilage and on the ligatures and disturbs the bronchial arteries and peribronchial tissues to the least degree. An alternate, simple method and one often used clinically, is that of inserting one or two layers of vertical mattress sutures so as to approximate the flaccid portion to the anterior arch. This has two disadvantages, namely there is a danger of catching a bronchial artery in a suture and occluding it and there is considerable disturbance of the peribronchial tissues. It may even lead to a further disadvantage as illustrated by dogs #10 and #20. In dog #10 such a method was employed while in dog #20 a mass ligation technique was used. Because a small amount of bronchus necessarily extends out beyond the point of occlusion a cyst, as developed in dog #20 and as suggested in dog #10, could result. This complication resulting from closure of a bronchial stump has not hitherto been reported.

No mention has been made of curettage or cauterization of the bronchial mucosa prior to occlusion of the stump. Previous experience has demonstrated that this offers little, if anything, and could well be dangerous in that either procedure causes an inflammatory reaction which might delay further the already slow process of healing. In addition, as so little of the healing occurs in the submucosa, due probably to its meager blood supply, there would appear to be little advantage offered by either of these procedures.

Although from these experiments there is no proof to support such a supposition, for the results were equally satisfactory whether or not the stump was covered by pleura or buried in the mediastinum, it would seem logical that covering or burying the stump is an advantage. This permits it to be completely covered by loose vascular mediastinal tissue and by pleura, which may reinforce it as well as supply further blood by acting as a graft.

These experiments have disclosed one further interesting and possible complication associated with closure of the bronchial stump. In dog #15 a low grade, inflammatory granulomatous mass developed from the fibrous cap and protruded into the lumen of the stump (Fig. IV). This was soft, friable and very vascular and one could picture a considerable amount of bleeding arising from such a lesion. In all probability the puddling of secretions with attendant bacteria played a part in the development of this complication.

<u>Summary:</u>

The literature concerning the methods of closure and

the process of and factors influencing healing of the sectioned bronchus has been briefly reviewed. The facts of importance, revealed by this, have been summarized.

The materials and methods employed in this investigation have been described in detail. Illustrations in the form of photomicrographs and one chart have been included to demonstrate some of the points discussed in the text.

Although there is little to be added to the existing literature, the factors of importance in securing healing, as reported by Longacre (49), have been confirmed. The use of a minimal quantity of relatively inert, non-absorbable suture material in the bronchus is stressed.

Although in small animals, with soft, relatively non-resistant bronchi a mass ligation technique of the hilus can be employed with satisfactory results, it is not recommended for larger animals including man. The reasons against using it have been presented. The individual dissection and ligation technique has been proven as the method of choice by reports in the literature. This was confirmed by these studies.

As to the actual closure of the stump, the necessity of preserving the bronchial artery blood supply, which is acknowledged by anatomists as being almost the sole supply to the bronchus, is stressed. Similarly the preservation of the peribronchial tissues with as little disturbance of them as is feasible is recommended, for it is from here that healing occurs through the formation of a dense fibrous cap over the end. There is little of the healing process originating in the submucosa. Thus, in closing these large bronchi, it is suggested that the sutures used must not be under great tension, and must not disturb the blood supply. Furthermore as they give rise to a certain amount of reaction, which in all probability delays healing, the minimal amount of suture material compatible with air-tight closure should be used by the surgeon. The only practical means of obtaining air-tight closure with the minimal amount of stress on the sutures and pressure on the cartilage is through approximation of the flaccid portion of the bronchus with the anterior arch. The simplest method, which observes all the principles outlined, is the method of closure by means of over-end silk sutures. The use of interrupted mattress sutures has been discussed and the disadvantages considered. The possibility of a cyst of the stump has been cited.

It has been demonstrated that healing of the sectioned bronchus is slow and is not secure in the healthy animal for at least three weeks after operation and that during this period the ligatures are tending to cut through. Thus any complication which delays this healing would be a factor in causing a broncho-pleural fistula to develop.

It has also been demonstrated that in most instances in the case of the larger animals where a main stem bronchus is divided and the proximal end sutured closed, the sutures eventually either cut through or break so that the lumen assumes its normal shape and the maintenance of air-tight closure becomes entirely dependent upon the fibrous cap. On the other hand, in the small animals, the ligature, when the mass ligation technique is employed, maintains closure for a longer period and is gradually replaced by fibrous tissue along with the formation of the cap so that the stump here has a tapered appearance.

The question of cauterization or curettage of the bronchial mucosa, prior to closure of the stump, has been considered. Although this was not studied it would seem unwarranted because in the first place the submucosa plays little part in the healing mechanism and secondly, as Longacre (49) has suggested, an inflammatory reaction may delay healing and such a reaction could be expected when either cautery or curette is used.

The question as to whether or not the bronchial stump should be buried in the mediastinum or, if this is impossible, covered with pleura, has been discussed. Although the experiments seemed to indicate that it didn't matter whether it was or not, it seemed logical to the author that covering or burying the stump has an advantage in that it reinforces the stump with tissues which may perhaps add a little to its already meager blood supply.

Another, possibly serious complication of lung resection was suggested by the finding of a soft, very vascular granulomatous lesion in the lumen of the stump in one animal. This arose from the fibrous cap. Its appearance suggested that considerable bleeding could arise from here. The pathogenesis of this was proposed.

The important point brought out by these experiments was that if all the factors concerned in the mechanism of healing are observed, the incidence of reopening of the stump will be minimal for out of twenty-three animals upon which pneumonectomy was performed not one case of broncho-pleural fistula was encountered.

Conclusions:

1. A review of the literature has demonstrated that

absorbable sutures should never be used to close a bronchus, where permanent closure is sought.

2. A review of the literature has disclosed that there has been no one satisfactory method of closure of the bronchial stump which guarantees permanent closure.

3. A review of the literature has shown that a mass ligation technique of the hilus, in lung resection, is unsatisfactory and results in a high incidence of broncho-pleural fistula. Experiments here, however, have clearly demonstrated that this method is entirely satisfactory for small animals with soft, non-resisting bronchi. It is agreed, however, that this method is not to be recommended for larger animals.

4. These experiments have confirmed the observations of previous investigators that healing of the bronchial stump is, for the most part, through the formation, from the peri-bronchial connective tissue, of a fibrous cap over the cut end.

5. There is some healing across the submucosa but this is of no significance.

6. The healing process is slow and requires, in healthy animals, over three weeks from the time of operation

before it is secure and no longer dependent upon the sutures.

7. The sutures have a tendency to gradually cut through the bronchus. The tighter they are tied and hence the greater the pressure they exert on the cartilages, the sonner will they cut through.

8. The sutures eventually cut through the large elastic bronchi and the stump generally takes on a squared or ballooned-end appearance.

9. In smaller animals because there is little pressure required to occlude the bronchus the ligatures will generally not cut through and the stump heals with a resultant tapered appearance.

10. The use of interrupted mattress sutures placed parallel to the long axis of the bronchus could well interfere with the healing process through interruption of the blood supply to the stump and might also result in the formation of a cyst of the stump.

11. Burying the stump in the mediastinum or covering it with a leaf of pleura is probably desirable, but there is no proof of this.

12. Curettage or cauterization of the mucosa of the stump prior to closure is undesirable.

13. A complicating bleeding granuloma may develop in the stump of the bronchus and give rise to serious complications.

14. The principles suggested by Longacre (49) that if followed would lead to a minimal incidence of postoperative broncho-pleural fistula in lung resection, appear to be confirmed by the results of these experiments.

CHAPTER III

INTRATHORACIC READJUSTMENTS FOLLOWING PNEUMONECTOMY

Introduction:

There has been considerable discussion amongst thoracic surgeons as to whether or not a thoracoplasty should be performed immediately following pneumonectomy in order to diminish the space created. In part, the argument has been that the readjustment of the thoracic organs necessary to obliterate this space is perhaps injurious and hence undesirable. Evarts Graham (32), in discussing Reinhoff's paper (69) in 1936, has stated, and this is borne out by the experience of others, that 'it is a fairly common experience to find that patients with chronic fibroid tuberculosis sometimes suffer from disabling dyspnoea'. This he attributed to the marked displacement of the trachea and great vessels to one side. Such patients, he added, showed an amazing improvement in the dyspnoea following a thoracoplasty because it permitted the trachea and vessels to assume their normal positions. This he held as an argument in favor of performing an extensive thoracoplasty following pneumonectomy for here there is always a marked displacement of mediastinal structures to the operated side.

Although it is fully realized that the readjustment of thoracic organs following pneumonectomy in animals do not compare in their entirety with those in man, it is felt that some understanding of these changes is necessary before one of the main subjects of this thesis, namely the fate of the remaining lung, is approached. Thus was this study undertaken.

In reviewing the literature it was soon realized that the readjustment of thoracic organs in the pneumonectomized dog have been well described. It was still felt, however, that a reconsideration would be of interest. Furthermore, there have been no reports of changes in the cat, and as many pneumonectomies were performed here on cats it seemed not amiss to study them and make a comparison with the dog. Similarly, as a few rabbits were pneumonectomized, they also were studied for purposes of comparison.

Historical:

Haasler (34), in 1892, was the first to describe the intrathoracic readjustments in dogs and rabbits following pneumonectomy. His descriptions however were quite incomplete. In 1906, Hellin (38) mentioned the changes occurring within the rabbit, but not in any detail. Other such reports followed.

Friedrich (26) mentioned the changes in the pneumonectomized dog, Quinby and Morse (67) also in the dog and Da Fano (21) in the rabbit. Their descriptions were all much alike but were not detailed. Kawamura (44) published the first really thorough account of the changes occurring within the chest of the pneumonectomized dog.

After the one lung had been excised, and while the chest was still open, he observed a rather marked expansion of the contralateral lung associated with a shift of the mediastinum to the operated side. Between five and thirteen days postoperatively the dogs showed a rather active respiratory excursion with bulging and broadening of the intercostal spaces on the unoperated side, whereas the operated side barely moved, was more or less flattened and had narrowed intercostal spaces. On sacrificing the animals and autopsying them, he observed that the diaphragm was higher on the operated side, the heart and mediastinum shifted over towards it and a compensatory expansion of the remaining lung resulted in a portion of the lung partially covering the anterior surface of the heart. The pleural cavity was thus considerably diminished and no fluid was present within it.

In the dogs sacrificed between fifteen to thirty days postoperatively, the changes which he observed were even more remarkable. The bulging of the thoracic cage on the unoperated side was very conspicuous, particularly in comparison with the sunken, flat appearance of the operated side. The diaphragm on the operated side had ascended still higher and in addition the dome of the pleural cavity appeared to have descended somewhat. This decreased pleural space was almost completely filled by the heart, great vessels, oesophagus and remaining lung. The heart had shifted laterally and rotated posteriorly so that the pericardium lay very close to the chest wall. It was completely covered anteriorly by a herniation of the anterior portion of the remaining lung.

Within thirty to sixty days after pneumonectomy, he noted that the pleural space, created by the excision of the lung, was generally completely filled through the above described compensatory changes. Later still, he observed a gradually developing scoliosis, which in time became fairly marked.

With the development of the Roentgen ray some further details were added and a few minor points of Kawamura's observations contradicted. Heuer and Dunn (40) studied pneumonectomized dogs by means of fluoroscopy and autopsy. Contrary to Kawamura they noted that unless the diaphragm was paralyzed, it played little part in the obliteration of the cavity. If the phrenic nerve was not interfered with at the operation, the diaphragm did not become elevated and its movements remained synchronous with those of the unoperated side. The upper portion of the remaining cavity became obliterated through a herniation of the upper lobe of the remaining lung through the anterior mediastinum, whereas the middle lobe often extended far to the operated side, across the midline, anterior to the heart, to fill the anterior portion of the inferior part of the space. The larger portion of the lower part of the space, between heart and costo-diaphragmatic sulcus was obliterated by a herniation of the lower lobe through the mediastinum between inferior vena cava and vertebral column. So far as a scoliosis was concerned, they found that this was confined mainly to the upper thorax.

Concerning the only significant divergence of opinions in Kawamura's and Heuer's and Dunn's studies, namely the part played by the diaphragm in obliterating the space, Behrend and Mann (7) confirmed the latter's observation. While Heuer and Dunn and Behrend and Mann were careful to point out that the phrenic nerve was not interrupted or traumatized during the operation, Kawamura makes no mention of it. Thus it is quite possible that in his animals the phrenic nerve was interrupted, and thus the divergence of opinions would be explained.

Such, according to the literature, are the changes which occur within the thorax of the dog following pneumonectomy. Rats (41), and rabbits (21) reportedly show essentially the same anatomical readjustments.

Materials:

The animals employed in this study, for the most part, were those used in the bronchial stump series which were sacrificed. These numbered, all told, 4 dogs, 7 cats and one rabbit. On these, detailed examinations including x-rays and fluoroscopy, were performed. The remaining 12 animals, all of which died from various causes, were examined only at autopsy. There were eleven right and twelve left pneumonectomized animals.

Methods:

The animals, while alive, were observed for any evidence of compensatory readjustments. Following this and for more detailed studies in the living animals, the x-ray was extensively employed. All these animals were examined by means of anteroposterior and lateral films of the chest. In addition fluoroscopy was performed in all the dogs and cats prior to sacrifice. In 4 dogs and 3 cats under deep nembutal anesthesia, so that respirations were slowed to a rate of 5 to 10 per minute, a fine urethral catheter was inserted intratracheally and, under fluoroscopic guidance, lipiodol was then slowly injected in order to outline the bronchial tree of the remaining lung. X-rays in the expiratory and inspiratory state were taken of the animals both in the anteroposterior and lateral positions in order to study distribution of the bronchi. Deliberate flooding of the alveoli was then encouraged in order to demonstrate clearly, if possible, any herniations of the remaining lung into the operated side. In three of the adult dogs, in order to study the effects of pneumonectomy upon the bronchi of the remaining lung, a lipiodol study was performed upon the right lung prior to operation. X-rays were taken in the right lateral position on expiration with the x-ray tube at a constant distance from the cassette. Prior to sacrifice, and approximately three months postoperatively, this study was repeated on the remaining lung in the same manner, the x-ray tube being centered upon approximately the same fixed point on the chest and the same distance exactly from the cassette. The preoperative and postoperative films of the lung were then compared and measurements taken of the diameter and length of bronchi from the same fixed points in the bronchial tree.

All animals, both those which died from various causes and those sacrificed, were autopsied in a similar manner. The method of sacrificing consisted of very deep intraperitoneal, supplemented by intravenous, nembutal anaesthesia in the cats and deep intravenous nembutal anaesthesia in dogs and rabbits. In all, the anaesthesia was carried almost to the point of death. The animal was postured on the table in a supine position. The trachea and great vessels of the neck were exposed and, while in deep inspiration, all were clamped simultaneously. Following death the thorax was immediately opened by removing the sternum and ribs to about the midline laterally. The anatomical readjustments were then studied, and photographs taken. The clamp was then released from the trachea and the lung permitted to collapse. The consequences of this manoeuver were observed and some of the animals photographed for purposes of illustrations. After removal of the remaining lung and mediastinal structures en masse, the thoracic cage and spine were examined for evidence of scoliosis, narrowing or widening of the intercostal spaces and other abnormalities.

Results:

In embarking upon this study, the factor of time required for readjustment of organs was not studied in particular, because we wished to have the animals survive for as long as possible in order to make the studies on the changes occurring in the remaining lung. This factor of time, however, has been fairly thoroughly worked out through the studies of others, namely, Kawamura (44) and Heuer and Dunn (4). We did, however, observe in our animals sacrificed at one to three months postoperatively that the readjustments were generally complete except for the factor of scoliosis. Also the few animals which died from various causes in the earlier postoperative period confirmed the findings of previous investigators regarding the time element. This time factor is of importance in the discussion of the fate of the remaining lung and will be referred to again in the chapter devoted to this problem. Thus the purpose here is to merely describe the anatomical readjustments subsequent to resection of one lung.

The findings in the dog and the rabbit are essentially the same, but differ in some respects from those occurring in the cat. In the early and late periods all animals showed a slight flattening of the operated side, and slight to moderate bulging of the healthy side. Similarly, respiratory movements were more apparent on the healthy side than on the operated. In the late periods, all revealed a mild scoliosis with the concavity towards the operated side. This appeared almost wholly confined to the upper one-third or one-fourth of the thoracic spine. As a matter of fact, had one not been carefully looking for a deformity, resulting from the operation, one would have judged, at a cursory glance, that the animals were entirely normal, so minimal was the deformity, particularly so in the small animal.

Fluoroscopic, x-ray and lipiodol studies proved very interesting in respect to the thoracic organs as a whole. The cavity of the operated side appeared diminished in size due mainly to a narrowing of intercostal spaces, whereas, on the unoperated side it appeared larger than normal as a result of widening of intercostal spaces. There was invariably a marked shift of the mediastinum towards the operated side. The heart in all instances was observed to be shifted so that it lay up against the chest wall on the operated side. The unoperated side on the other hand appeared completely filled with lung. The operated side was also filled with thoracic organs except at the costo-phrenic angle. Lung tissue appeared to fill the small space remaining in the upper portion of this cavity. Similarly lung tissue appeared to extend anteriorly across the midline and in front of the heart to occupy the anterior portion of this space. The picture in the dog and the rabbit, however, differed from that in the cat in the remaining lower one-third of the cavity. In the dog and rabbit a large herniation of lung appeared to extend across beneath the heart into here whereas in the cat such was not

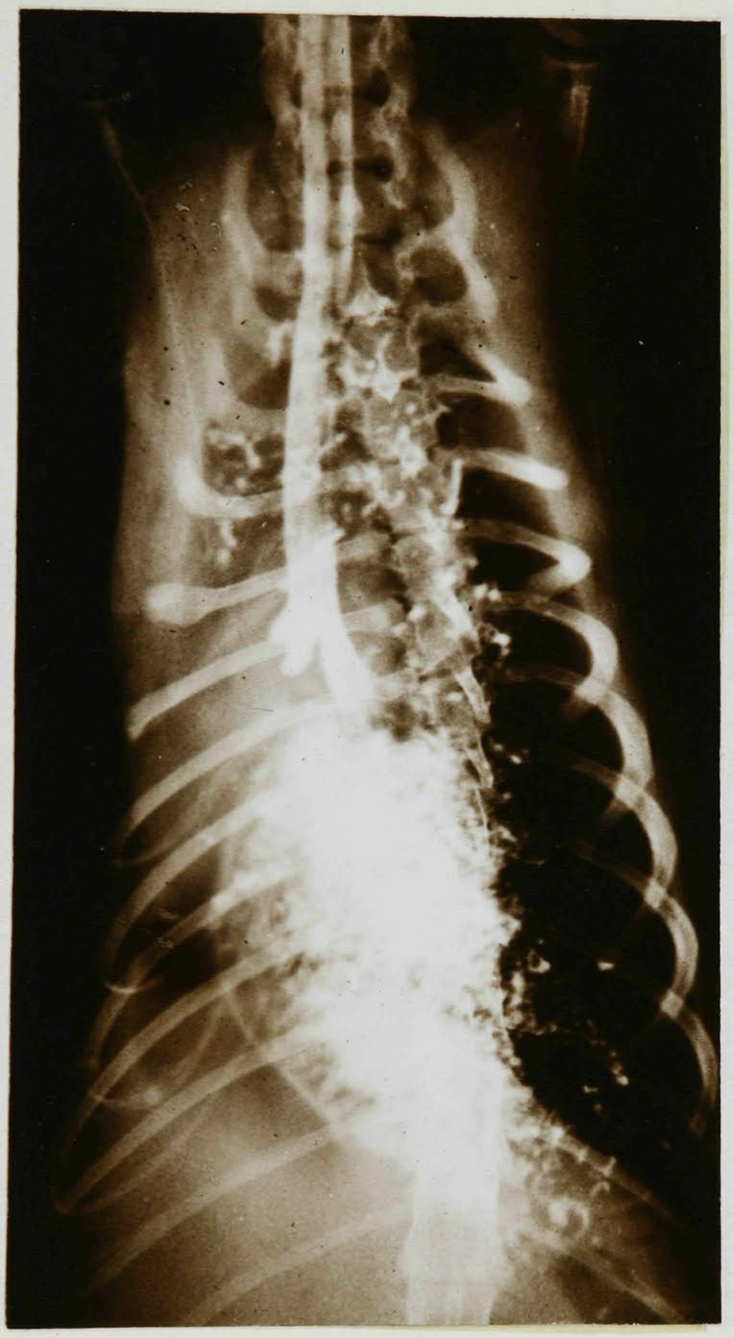


Figure XI

Cat #87. 1 year after right pneumonectomy. Lipiodol study.

Note: 1. Shift of mediastinum to operated side.
2. Herniation of remaining lung into superior portion of operated side.
3. Large herniation flooded with lipiodol extending across in front of heart into inferior portion of operated side.
4. Dead space at costo-phrenic angle on operated side.

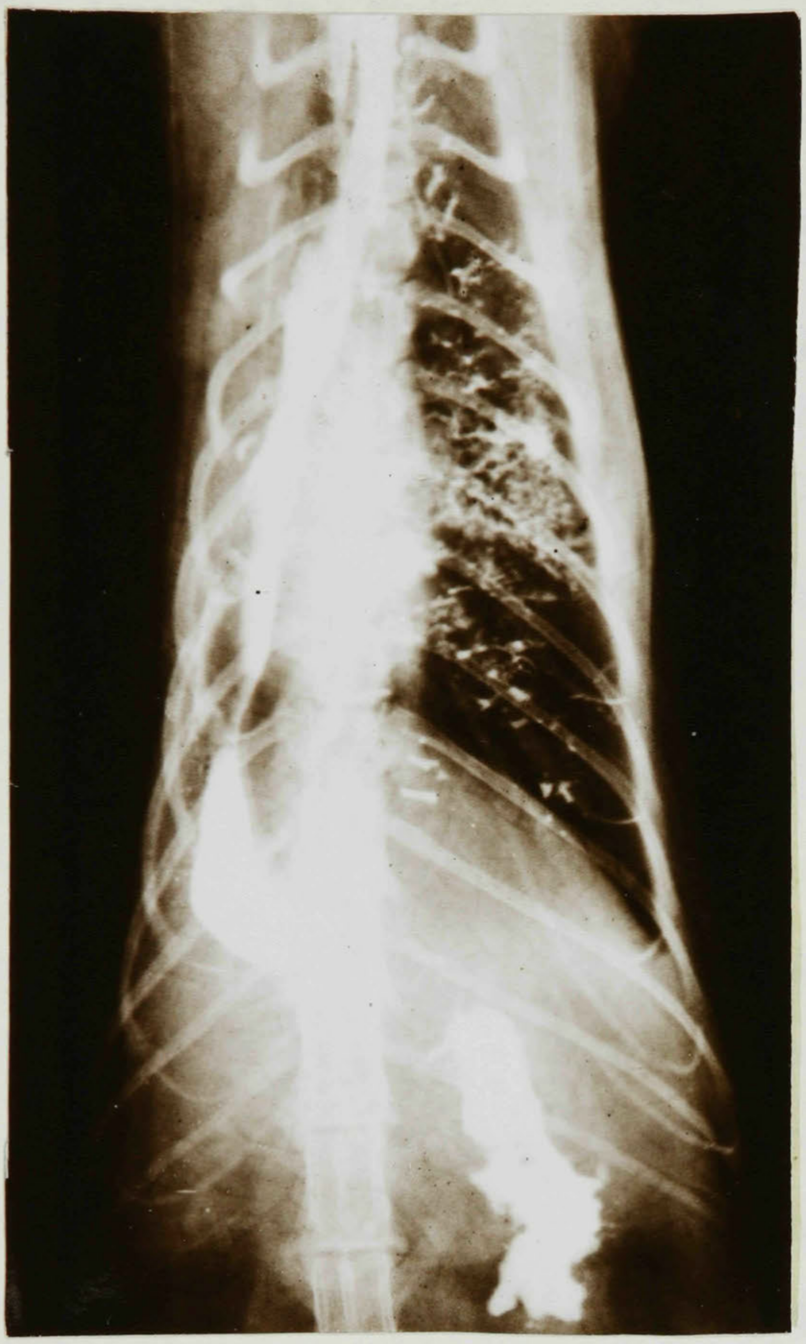


Figure XII

Cat #88. 1 year after right pneumonectomy. Lipiodol study

Note: 1. Shift of mediastinum and herniations of lung.
2. Displacement of oesophagus with dilatation of the lower one-third.

observed. The domes of the diaphragm were in normal position on both sides and their movements were equal.

The lipiodol studies, to outline the herniations by flooding, confirmed the above described picture (Figs. XI and XII). In addition, in some of the animals the lipiodol regurgitated through the bronchi and trachea into the pharynx and was swallowed. Thus the oesophagus was well outlined. It was markedly deviated towards the operated side in all instances and in two cats the lower third appeared considerably dilated (Fig. XII).

Autopsy of the cats confirmed the radiological studies. Upon removing the sternum in those animals in which the right lung had been excised only lung presented (Fig. XIII). The right ventricle was just visible and was lying up against the lateral chest wall (Fig. XIII). The heart, on closer examination, was found to be shifted laterally and rotated in a clockwise direction so that it occupied a portion of the postero-lateral area of the operated hemi-thorax. An unoccupied space was observed at the costo-phrenic angle. All three lobes of the remaining lung were herniated through the anterior mediastinum to fill the anterior portion of the chest on this side (Fig. XIII). Posteriorly, the oesophagus was pulled over markedly. The inferior mediastinum between the spine and

Figure XIII

Cat #84. 1 year after right pneumonectomy.
Autopsy specimen with lung inflated

Note: 1. Tremendous size of lung with herniations into operated side.
2. Right ventricle of heart just visible.
3. Unoccupied space at costo-phrenic angle.

Figure XIV

Cat #84. Remaining lung in collapsed state.

Note: 1. Size of collapsed lung.
2. Adhesion mooring mediastinum to chest wall.

inferior vena cava was bulging in this direction but it could hardly be considered a true herniation of lung.

The cats upon which a left pneumonectomy had been performed displayed an essentially similar picture, except that upon opening the chest more of the anterior surfaces of the heart was visible and, due to its normal anatomical position, it did not reveal the same degree of rotation and displacement as observed in the case of right pneumonectomy.

Upon releasing the clamp from the trachea the remaining lung was seen in all instances to spontaneously collapse to a size slightly larger than normal. Except in those instances in which the mediastinum was anchored to the lateral chest wall on the operated side, through adhesions (Fig. XIV), the mediastinum and heart returned to a normal position.

The dogs and rabbits on the other hand, at autopsy, revealed a slightly different appearance. In both, the shift of the mediastinum and anterior herniations of the lung were the same as in the cat (Fig. XV). The unoccupied costo-phrenic space was smaller. The striking difference occurred in the mediastinum beneath the heart. Here a large herniation of the cardiac or lower lobe of the remaining lung extended into the

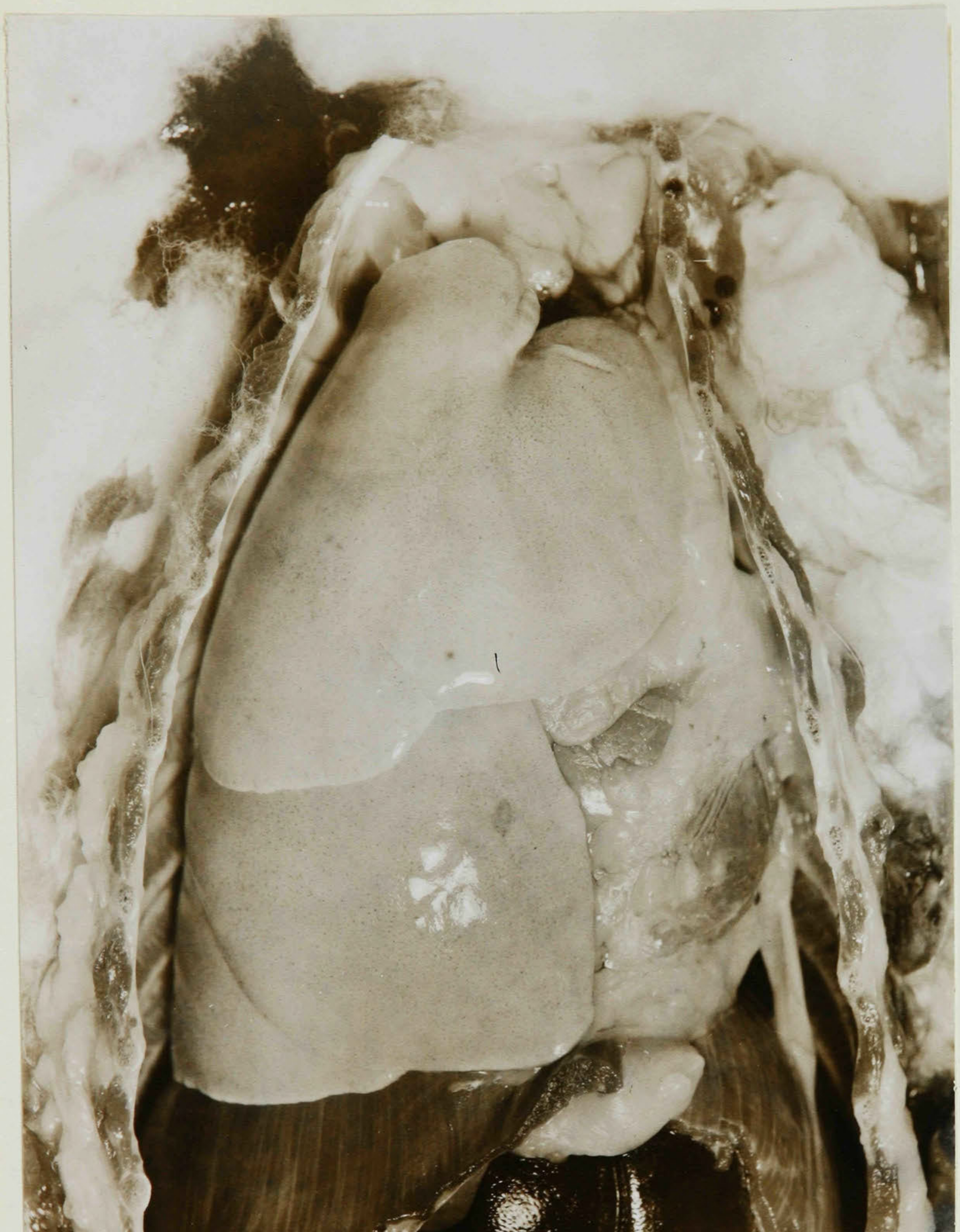


Figure XV

Dog #20. 18 months after left pneumonectomy.
Autopsy specimen with lung inflated.

Note: 1. Shift of mediastinum.
2. Enlargement of lung and herniations.
3. Dead space at costo-phrenic angle.

Figure XVI

Dog #20. Remaining lung in collapsed state.

Note: 1. Size of collapsed lung.
2. Adhesion moorning mediastinum to chest wall.

Figure XVII

Rabbit #77. Four months after left pneumonectomy. Left lateral view of autopsy specimen with lung inflated.

Note: Large herniation of lung beneath heart.

operated side between the vertebral column posteriorly and the vena cava anteriorly (Fig. XVII). This tended to fill the larger portion of the posterior region of the costo-phrenic sulcus and also seemed to lift the heart superiorly and anteriorly so that the heart literally was sitting upon a pillow of aerated lung. A careful comparison between dog and rabbit and the cat revealed a much more flaccid mediastinum in the first two than in the third. The mediastinum in this region was very thin in the dog and rabbit whereas in the cat it was thicker and more resistant. This, then, probably accounted for the herniation in the one group and not in the other.

Upon releasing the clamps from the trachea in both dogs (Fig. XVI) and rabbits the remaining lung reacted as in the cat and when no adhesions existed between the hilus and the chest wall the heart and mediastinum returned to their normal positions.

After the thoracic organs had been removed en masse, an examination of the thoracic wall and spine in all animals confirmed the previous observations as to the contraction of the operated side through a narrowing of the intercostal spaces and a scoliosis of the upper dorsal spine. The deformity could be considered minimal. The domes of the thorax differed only slightly on each side. That of the operated side appeared slightly smaller and lower while that of the unoperated side appeared slightly larger and higher than normal, which is in fitting with the attempt of the body to decrease the space created by the loss of a lung.

The lipiodol studies on the effects of the excision of one lung in the dog upon the diameter and length of the bronchi of the remaining lung revealed no measurable change in diameter or length of the larger bronchi when the preoperative and postoperative films were compared. Some of the smaller bronchi of the remaining lung appeared slightly wider than normal, however.

Discussion:

The anatomical readjustments occurring following the excision of one lung in dogs, cats and rabbits essentially follow the pattern described by Kawamura (44) in 1914. In certain respects, however, our observations conflict with his and confirm those of Heuer and Dunn (40). The diaphragm, which Kawamura stated ascended to decrease the superior and inferior diameter of the operated side was found not to occur in the studies of others (40),(7). The present investigation revealed no noticeable change in either position or movement of the leaves of the diaphragm. Kawamura did not state whether or not the phrenic nerve was traumatized and it is possible that this might have been the case thus explaining discrepancy in his observations as compared with others.

Again he stated that the deformity of the thoracic cage became quite marked in time. He was using large dogs and it is quite possible that he observed a greater degree of deformity than was observed in these experiments in which most of the animals were of small size. Certainly, had one not known upon which side the pneumonectomy had been performed, one would experience great difficulty in determining from which side the lung had been removed, so minimal was the deformity. In the cats and rabbits it was relatively non-existent and only by means of fluoroscopic, x-ray and autopsy examinations did it become clearly apparent in these small animals. The scoliosis as in the case of Heuer's and Dunn's studies was found to be confined mainly to the upper thoracic spine. This compensatory mechanism is undoubtedly an attempt by the animal to decrease the size of the space created by the loss of one lung.

Contrary to all previous investigations, the present studies disclosed a persistence of a dead space in the costo-phrenic sulcus. This was larger in proportion in the cats than in the dogs and rabbits. The explanation of this variation lies in the anatomical structure of the inferior mediastinum of these groups of animals. In dogs and rabbits the posterior portion of the inferior mediastinum is very thin and flaccid. The mediastinal pleura of the two sides comes together at this point and consequently there is little resistance to prevent a herniation of the lung. Therefore in both dogs and rabbits a large herniation of the cardiac or lower lobe extends through this point into the operated side and fills most of the inferior portion of the cavity. In cats, however, the mediastinum in this region is more rigid and resists any attempted herniation on the part of the remaining lung. Thus all that can be seen in the animals is a bulging of the mediastinum towards the operated side between spine and inferior vena cava. The result is that the dead space in the costo-phrenic angle is larger in proportion than in either the pneumonectomized dog or rabbit.

The anatomical readjustment within the thorax of the pneumonectomized human have been described by Rienhoff (67, 70). When compared with the cat they are seen to be quite similar for in the human there is also no significant herniation through the inferior mediastinum.

In these papers Rienhoff also describes the formation of a 'space occupying fenestrated labyrinth of connective tissue', occupying a large portion of the hemi-thorax from which a lung has been excised. He states that following pneumonectomy a sero-sanguineous effusion immediately develops in the space. After some hours, coagulation of the main portion of this occurs. The precipitated fibrin, he claims, forms a fragile scaffolding which in time is organized by fibroblast growing in from the chest wall, so that what at first was a homogeneous mass of fibrin becomes transformed into a multi-loculated, space-enclosing, honeycombed mass of fibrous tissue which contains, in turn, fluid in small labyrinthian-like spaces. This mass is supposed to act as a filler of the space not occupied by the compensatory dilatation of the remaining lung. Rienhoff further declares that the formation of this sero-sanguineous exudate seems to be the 'modus operandi' by which the body tends to obliterate dead or empty spaces created within its confines.

In the animal experiments of others, as well as those herein reported, no such effusion is common postoperatively provided that the operation is performed with the minimum of trauma and infection avoided. No one has reported observing this 'fenestrated labyrinth of connective tissue' in animals following lung resection. Although in the pneumonectomized cats a relatively large dead space exists on the operated side more than one year after operation, this remains entirely empty. The pleura in this area is normal in appearance as elsewhere. Certainly in animal experimentation one can conclude that there is no such 'modus operandi' as described by Rienhoff as occurring in man.

Rienhoff in the same papers has stated that in man, at least, following right pneumonectomy the remaining lung may not be able to cross the midline and fill the opposite side of the chest as in the case of the right lung in left pneumonectomy. Furthermore he contends that the displacement and rotation of the heart to the left are mechanically easier of accomplishment than to the right. This latter statement seems logical but he goes on to say that if the rotation and displacement of the heart to the right were possible this might well give rise to a disturbance of the circulation, for, from the mechanical point of view, rotation of the heart to the left and posteriorly would cause much less disturbance in the angulation and twisting of the aorta than would the same degree of displacement to the right. Graham (32), in discussing Rienhoff's paper, has stated that 'it is a fairly common experience to find that patients with chronic, fibroid tuberculosis sometimes suffer from disabling dyspnoea because of the marked displacement of the trachea and great vessels to one side. In such patients a thoracoplasty nearly always results in an amazing improvement in the dyspnoea because it permits the trachea and great vessels to assume their normal position'. Certainly in the experiments performed here, following right pneumonectomy, the mediastinum shifted markedly to the operated side and the heart was considerably displaced laterally and rotated posteriorly. Anterior herniation of the lung occurred as readily in right-sided pneumonectomy as in left. As far as could be determined there was no apparent disability or complication as the result of this displacement. Graham's statement, although concerning humans, would seem to be refuted by these animal experiments. However one cannot safely draw conclusions from experimental work in animals and apply them to man. There are many other possible explanations of the phenomenon described by Graham.

Radiologists are quite aware in man, and it was observed on fluoroscopy of the dogs prior to operation, that during respiration the bronchi appear both to increase in diameter and length. No mention has been made in the literature of the effects of pneumonectomy upon the larger bronchi from this point of view. Lipiodol studies performed on dogs pre- and postoperatively demonstrate conclusively that the larger bronchi, that can be visualized by the use of contrast media and x-rays, despite the tremendous increase in the size of the remaining lung, show no measurable change in either diameter or length. The smaller bronchi, on the other hand, may become slightly widened but not appreciably lengthened. Any actual differences, however, could be considered too minimal to be of significance. It would seem that, although on inspiration, probably through an intrinsic action, the bronchi increase in length and diameter, in the remaining lung they are essentially unaffected by the distension to which this organ is subjected.

The time required for these readjustments, particularly the obliteration of the cavity created by the excision of one lung, is important in a consideration of the fate of the remaining lung. This has been adequately studied in dogs by Kawamura (44), Heuer and Dunn (4), and Behrend and Mann (7). To all intents and purposes, within thirty days after operation the intrathoracic readjustments are completed. The lung by this time has almost reached its maximum degree of distension. The animals which were studied one to three months postoperatively confirmed this fact. This rapidity of readjustment, particularly the enlargement of the remaining lung, might well explain some of the conflicting observations reported concerning the fate of the remaining lung, to be discussed in a subsequent chapter. The mechanism of the compensatory readjustment of organs within the thorax depends upon the absorption of air from the cavity created by the operation. There consequently develops a negative pressure of greater degree in the cavity than in the opposite pleural space. Thus the heart and mediastinum are drawn towards the operated side and the herniations follow.

The presence of a dilated oesophagus in two animals requires explanation. The mechanism is obscure. It could be that, in the performance of the operation, the vagus nerve was inadvertently interrupted thus interfering with part of the nerve supply to this organ which in turn might result in this complication. It is significant that these animals showed no disability from this condition.

<u>Summary</u>:

The literature concerning the anatomical readjustments of organs following the excision of one lung in dogs, rabbits and cats has been briefly reviewed.

The materials and methods employed in this investigation have been described in detail. Photographs of x-rays and autopsy material have been included to illustrate, as nearly as possible, the various points brought forth in the text.

These studies in dogs confirm in every respect those of Heuer and Dunn (40) and Behrend and Mann (7). The mild degree of actual bony cage deformity is stressed. The investigations carried out on rabbits demonstrate that the deformity is almost negligible and that the intrathoracic readjustments closely simulate those in the dog. These, briefly, consist of a shift of the mediastinum towards the operated side, due to the differences in intrapleural pressures between operated and unoperated sides, accompanied by a lateral displacement and posterior rotation of the heart. In addition to anterior herniations of the upper three lobes across the midline to fill the anterior portion of the cavity, there is a large posterior herniation of the cardiac or lower lobes between the vena cava anteriorly and the spine posteriorly. This fills a large portion of the posterior-inferior region of the chest on the operated side. A small dead space still persists at the costo-phrenic angle.

Cats do not show the same changes as in the dog or rabbit. The main difference concerns the posterior herniation. Due to more resistance of the mediastinum in this area in the cat than in the dog or rabbit, a definite herniation of the lung into the posterior-inferior portion of the operated side is prevented. All that can be seen is a bulging of the mediastinum. Consequently, the dead space is proportionately larger in this animal. The anterior herniations, however, are similar to the other animals. The similarity between the changes in the cat and those in the human is mentioned.

In all animals, when the air is released from the lung the mediastinum and heart spontaneously return to their normal position, unless adhesions prevent. In the animals which have survived for over one year, the remaining lung still collapses spontaneously to reach a size slightly larger than a comparable collapsed lung of the normal.

The existence of Rienhoff's 'space occupying, fenestrated labyrinth of connective tissue' has been shown not to develop in the experimental animal and doubt has been cast upon his supposition that an effusion is the 'modus operandi' by means of which the body obliterates the space.

Contrary to Rienhoff's assumption (69, 70) and Graham's comments (32), the displacement of the heart and mediastinum to either right or left side causes no apparent disability, at least in the experimental animal. The amount of rotation which occurs does not appear to embarrass the circulation. However, it is stressed that due to the great difference in the anatomy of cats, dogs and rabbits and the human, one must hesitate in applying these observations to man.

These studies have further demonstrated that, following the excision of one lung, the length and diameter of larger bronchi of the remaining lung are unaffected, but that the smaller bronchi are perhaps slightly wider than normal.

The time required for these readjustments to be completed was not investigated, for this has been adequately studied and reported by previous investigators (44, 40, 7). By one month after operation, to all intents and purposes, the intrathoracic readjustments can be considered complete. The few animals studied within one to three months postoperatively bore this out.

In two cats, upon which pneumonectomy had been performed over one year previously, the oesophagus, besides being displaced, was found to be considerably dilated in its lower third. The presence of this was not suspected prior to the lipiodol studies, for the animals thrived and ate normally. It is suggested that perhaps trauma to the vagus during the operation was responsible for this state.

Conclusions:

1. The anatomical readjustment of organs following the excision of one lung in the dog and rabbit are essentially similar. However in the cat there is one marked difference,

which is accounted for by the structure of the mediastinum of this animal. No large herniation through the posterior portion of the inferior mediastinum develops as in the dog and rabbit.

2. A dead space remains in the chest on the operated side at the costo-phrenic angle in dogs, rabbits and cats and is relatively larger in the last than in the first two. This is due to the absence of a significant posterior herniation in the cat.

3. The intrathoracic anatomical readjustments in pneumonectomized cats more closely simulate those in man than do those in either the dog or rabbit.

4. The bony cage deformity is not significant in either dogs, rabbits or cats and is less apparent in the last two groups than in the first.

5. The greatly distended remaining lung of animals pneumonectomized more than one year previously collapses spontaneously when the chest is opened, to reach a size slightly larger than a comparable, collapsed normal lung. The mediastinum and heart, unless prevented by adhesions, return to their normal positions.

6. No effusion normally occurs into the space created by the removal of a lung in experiments upon dogs, cats and rabbits. No 'space occupying, fenestrated labyrinth of connective tissue', as described by Rienhoff (69, 70) as occurring in man, therefore appears. Doubt is thus cast on Rienhoff's assumption that the formation of fluid is the 'modus operandi' by means of which the body tends to obliterate an artificial space created within it.

7. The displacement of the mediastinum and heart have no apparent effect upon the circulation of the animal, as mentioned by Rienhoff (69, 70) and Graham (32) as a possible complication in the pneumonectomized man. Due to the difference in the anatomy between man and these lower animals, an application of these laboratory observations is not warranted.

8. The larger bronchi in the remaining lung show no apparent change in length or diameter. The smaller bronchi appear slightly widened but the degree of change is not significant.

9. The intrathoracic anatomical readjustments are, to all practical purposes, completed about one month postoperatively. Therefore the remaining lung must rapidly be over-distended.

10. Dilatation of the lower third of the oesophagus, without apparent disability, is occasionally observed in cats following pneumonectomy. The mechanism of this is not clear but possibly is a result of inadvertent damage to the vagus nerve during operation.

CHAPTER IV

THE FATE OF THE REMAINING LUNG

Introduction:

In the preceding chapter it was shown that the remaining lung enlarges to almost twice its normal size, in order that the space created, by the excision of one lung, may become obliterated. This great enlargement of the remaining lung has presented one of the most controversial problems in pulmonary surgery. It is apparent that most of the enlargement must be from distension and from here the conflicting opinions originate. There are those who present evidence to the effect that this distension is harmful and must be prevented, otherwise emphysema will surely result with subsequent pulmonary and/or cardiac failure. They therefore advocate an early thoracoplasty or other methods designed to prevent this. On the other hand, there are others who feel that emphysema does not develop in a previously healthy lung and that the remaining lung actually hypertrophies, thus anything which prevents this enlargement is deleterious. There are still others who have suggested that the lung actually grows or, in other words, becomes hyperplastic. This has, for the most part, been accepted in the case of growing animals but there are few, if any, who today believe that hyperplasia occurs in the lung of the adult animal, with the exception of the rodent family.

This present study is pursued in the hopes of clarifying the problem in the adult, so little mention will be made of the changes in the growing animals. Before, however, there can be any clear presentation of this problem it is necessary to present a clear definition of the terminology employed, for it is from a lack of this that so much confusion exists in the literature.

As, in general usage, the term 'emphysema' implies a pathological state it will be employed here in that sense only, namely, to describe, according to MacCallum (52), a condition of the lung in which there is a generalized over-distension of the functional respiratory units, with a marked stretching and thinning of their walls and with resultant impaired blood supply and nutritive changes. Either or both weaken the elastic alveolar wall, after a time, so that it remains permanently stretched or after breaking of its fibers gives way at one or more points. Such a state has been termed by MacCallum 'chronic substantive emphysema' and by others as 'chronic hypertrophic emphysema'. Grossly such a lung presents a typical pathological picture, being very voluminous but feeling soft and non-resilient and the characteristic crepitations felt on palpation of normal lung are so altered that one now experiences a feeling of bursting bubbles. In addition there is a peculiar pallor which is due to the obliteration of so much of the capillary bed. At times, large sacs or blebs may be present on the surface along the lung borders. However, the presence of blebs or sacs, per se, does not necessarily imply emphysema. Microscopically this lung reveals, as a most characteristic feature, large alveolar spaces with extreme thinness of the walls. With suitable stains a characteristic fragmentation of the strands of elastic tissue and narrowing and obliteration and even rupture of capillaries is seen. This, then, is the pathological picture, which in this study, the term 'emphysema' will be employed to describe.

In contradistinction to the term 'emphysema', we have chosen to use the term 'simple over-distension' to describe a condition of the lung in which there is a simple, mechanical over-distension which may include the larger bronchi and bronchioles as well as the functional respiratory units. In this condition, although there is the factor of dilated respiratory units with thinning of their walls, as in the case of emphysema, there are not the other characteristic gross and microscopical features upon which a diagnosis of emphysema is based. In the literature the term 'compensatory emphysema' has been employed to describe this state but because of the implications of the term 'emphysema' and its adjective 'compensatory' the term is both unsatisfactory and confusing.

The term 'hypertrophy' in the pathological sense denotes an 'enlargement and strengthening of an organ brought about by increase in size of its elements' (52). In this study it is applied to an organ composed of many units and is thus used in a slightly different sense, namely to describe an enlargement and strengthening of the lung brought about by an increase in size of the functional respiratory units and/or the conducting bronchi and bronchioles and larger blood vessels, et cetera. Thus, according to this definition, the 'increase in size' implies not only a dilatation or distension of the respiratory units, et cetera, but also a proliferation of the elements comprising these so that there is a 'strengthening of the organ'. As this is the sense in which the term 'hypertrophy' is used by those interested in this problem, and for want of a better term, it is retained here.

The term 'hyperplasia', as applied to the lung, is also somewhat confusing. In the true pathological sense it denotes 'a proliferation of the elements in response to a demand by the organ' (52). As applied to the lung, however, it is employed in a broader sense to describe not strictly a proliferation of the elements, but a proliferation of the functional respiratory units or alveoli. It is truly a 'compensatory overgrowth' of the remaining lung, but again it is a term which has been widely accepted and is therefore retained here.

If one thinks along pathological lines, one will encounter considerable confusion in reviewing the literature on this problem. However, bearing the above definitions in mind, one can analyze the various papers on the subject and readily interpret the conclusions. The literature has therefore been reviewed from this approach.

Historical:

Haasler (34), in 1892, using growing dogs and rabbits, studied the effects of pneumonectomy upon the remaining lung. He concluded that only in an occasional case could hypertrophy be observed. He found no evidence of hyperplasia. A few of his animals he followed up to seventeen months postoperatively.

Hellin (38), in 1906, on the other hand, concluded from a study of pneumonectomized rabbits, that the enlargement of the remaining lung was due to hypertrophy, perhaps also to hyperplasia, but definitely not to emphysema.

Möllgaard (56), in 1909, and Möllgaard and Rovsing (57), in 1910, reported the results of studies carried out on dogs. The conclusions they drew are quite confusing. From somewhat meager evidence they formulated that in old animals, if one part of the lesser circulation was put out of function, the undamaged part of the lung became distended and this persisted until the heart, by means of hypertrophy, mastered the demands placed upon it by this emphysema. On the other hand, in young animals they felt that hyperplasia assisted in the disappearance of the emphysema.

Da Fano (21), in 1912, in a study of pneumonectomized rabbits followed up to five months postoperatively, observed a gradual thickening of the alveolar septa with dilatation of existing capillaries and proliferation of new ones. He also observed an increase in the elastic fibers and a formation of rows of endothelial cells in the alveoli, which he interpreted as precursors of new alveoli. These changes he reported as beginning within six to ten days postoperatively and progressing steadily to reach a maximal development within five to six months. He therefore concluded that a definite hypertrophy of the lung took place and perhaps also a hyperplasia but definitely not an emphysema.

In 1914, Kawamura (44) published a most thorough study of this problem. He employed adult dogs and sacrificed them at varying periods up to six months after submitting them to pneumonectomy. His observations for the most part confirmed those of Da Fano, but are here reported because his histological studies are the most detailed that have been reported to date.

Within five to ten days after operation, he observed a gradual increase in the size of the alveoli, particularly those in the marginal regions of the lung. The alveolar septa were well preserved but the elastic fibers appeared thin. This he interpreted as being due to stretching. The elastic fibers of the pleura, however, actually appeared to be increased in number. The blood vessels during this period, more particularly the capillaries, were dilated. The collagenous tissue of the alveolar septa appeared essentially unchanged, but that of the pleura, like the elastic tissue, was increased.

Between ten to fifteen days postoperatively, he noted that the alveolar enlargement was more marked but that now newly developed fine elastic fibers could be seen traversing the septa in all directions, while those beneath the pleura were increased greatly in number. The blood vessels, although still considerably dilated, appeared to him to have increased in number.

The animals he sacrificed between sixteen and sixty days postoperatively revealed all the above changes to an increasingly marked degree. Now, however, the alveolar walls, instead of being thinned out by the alveolar distension, were thicker than anticipated and showed an increase in number and thickness of the elastic fibers which formed a definite network with fine meshes. This was most accentuated in the pleura and in the vicinity of the bronchi and bronchioles. According to him, these new fibers were in intimate relationship with the old and seemed to have originated from them. The blood vessels had ceased dilating, and there was now a very definite formation of new capillaries. The larger vessels revealed a thickening of the muscularis coat. The fibrous tissue elements were increased in amount in the same distribution as the elastic. A new manifestation was now apparent, namely, a dilatation of the bronchioles and alveolar ducts with a definite thickening of their muscular layer.

The animals which he sacrificed between sixty days and six months postoperatively, he stated, revealed a further thickening of the alveolar septa due to the proliferation of elastic and fibrous tissue elements and new blood vessels. Only occasionally did he observe a ruptured alveolus.

Kawamura stated that at no time did he observe any evidence to suggest a proliferation of new alveoli, nor did he find any evidence indicative of emphysema. It is apparent that, according to the definition previously recorded in this chapter, Kawamura observed hypertrophy of the remaining lung, if his observations are accurate. This is what he, himself, concluded.

There were no further reports on this subject until 1932 when Adams and Livingstone (3), in a study of eight pneumonectomized dogs followed up to one year postoperatively, concluded that the remaining lung tissue exhibited only varying degrees of 'compensatory emphysema'. From this article we conclude that, according to our definitions, they observed varying degrees of simple over-distension. Their report, unfortunately, is lacking in precise details.

Hilber (41), in 1934, reported some investigations carried out on pneumonectomized rats. He concluded that during the immediate postoperative period the increase in size of the remaining lung was due to simple over-distension, but that subsequently a true regeneration, in other words hyperplasia, developed. This may well be so, for as will be discussed later, the problem of growth in the rat is entirely different from that in the dog and cat, and probably in man.

Rienhoff, Reichert and Heuer (72), in 1935, published a report which has formed the basis of the controversy as to the fate of the remaining lung. This report was based upon a study of ten pneumonectomized dogs, and, because of its effect upon those interested in thoracic surgery, is here reported in some detail.

By means of control experiments they first determined the pressure required to distend a lung to its normal fullness and thereafter employed this pressure in fixing their excised lungs in the normal distended position. They then made various preparations of both control lungs and those under study. In several celloidin preparations they counted the branchings of the bronchi to the terminal air sacs and compared these figures with those obtained from comparable areas in the control lungs. In five different regions they demonstrated that the number of branchings were the same in the remaining lung as in the control. A similar count of the branchings of the blood vessels, although not as accurate due to the lack of a clear-cut end-point, revealed a close similarity between the abnormal and the control.

From studies of microscopical sections and models prepared from serial sections and compared with the controls, they concluded that there was only a very marked dilatation of the terminal respiratory units. From the constructed models they observed no difference between bronchial and vascular systems of the abnormal lung and the control. In their microscopical studies of the remaining lung, they reported that the alveolar septa were much thinner than normal and that the capillary bed embracing the alveoli was not increased but on the contrary the interstices in the plexus actually appeared larger than normal. As to the state of the elastic tissue, they felt that perhaps it may have been slightly, but only very slightly more sparse than in the specimens removed at operation. They emphasized that they did not observe any suggestion of absence or fragmentation of elastic fibers.

From these studies they concluded that the change occurring in the remaining lung following pneumonectomy consists of a simple dilatation of the functional respiratory units, which develops in response to increased physiological demands and is of a compensatory nature. To this they gave the name 'compensatory dilatation'. They also stressed that there was no evidence to suggest emphysema nor any to suggest hypertrophy or hyperplasia of the remaining lung.

In 1936 De Bernardis and Bracco (23) from Turin, Italy, reviewed the literature in conjunction with some experiments upon adult rabbits and dogs. Several Italian, French and German articles, to which we have had no access, were included in their review. Their microscopical studies would seem to be quite thorough. Their results confirmed those of Kawamura (44) in almost every respect. They likewise observed that there was an occasional rupture of alveolar septa, mainly in the marginal areas of the lung and that at times, even small blebs or bullae were present. They similarly concluded that a true hypertrophy of the remaining lung developed following pneumonectomy in the adult rabbit and lobectomy in the adult dog and that there was no evidence to suggest emphysema or hyperplasia in either.

Bremer (17), in 1937, from a study of one adult cat and one kitten pneumonectomized 'over one month previously' concluded that 'regeneration' occurs in the young and 'dilatation' in those whose lungs have ceased to grow.

Behrend and Mann (7) published in 1937 the results of some studies on pneumonectomized dogs sacrificed at periods from five days up to eight years postoperatively. All these animals were presumed to be adults. As in the case of most investigators they concluded that the remaining lung revealed no evidence of emphysema for they collapsed spontaneously upon opening the chest and displayed neither the gross nor microscopical features of emphysema.

They compared the weights of the right and left lungs of normal dogs and were able to arrive at a figure which they felt would permit an estimate of the weight of the remaining lung by merely weighing the excised one. Employing this method they discovered that the remaining lung was invariably heavier than the estimated weight. This they interpreted as being due to an increased amount of blood and to a proliferation of histiocytes.

From their microscopical studies they concluded that, for the most part, the size and thickness of the blood vessels were not materially changed from the normal except in those animals sacrificed within one week postoperatively. In these they felt that there was an apparent increase in the number of smaller vessels due to their engorgement with blood. In almost every autopsied lung they observed focal areas of proliferating histiocytes which manifested themselves as a symmetrical thickening of the normal alveolar walls. This feature was more obvious in the region of a bronchus. Although in the normal control lungs they frequently observed a similarly located infiltration of cells having the appearance of large lymphocytes, in the remaining lung the infiltration was composed of cells morphologically identical with histiocytes. As the postoperative period increased, these histiocytes, they stated, became smaller and their nuclei shrunken so that by eight years postoperatively they appeared to have been transformed into fibrocytes. Coincident with this ageing process of histiocytes, there was a proliferation of capillaries intertwining amongst these cells. This, they felt, increased to a considerable extent the blood supply of the lung. Although this vascular proliferation was observed as early as five days postoperatively, they remarked that it was strikingly apparent in the lungs of those animals sacrificed at later periods. They also stated that in the remaining lungs of animals sacrificed in the later post-operative periods, there was an increased amount of fibrous tissue and a marked increase in the reticular framework of the alveoli.

Although they employed a terminology essentially similar to that outlined earlier in this chapter, they concluded that 'hypertrophy, hyperplasia, emphysema, or even simple dilatation is not generally evident in the alveoli of the single lung remaining'. In a study of their results one would be inclined to disagree and to propose that there was some evidence suggestive of hypertrophy of the remaining lung, according to definition.

In 1940, Longacre and Johansmann (51) reported the results of similar invstigations on pneumonectomized puppies and adult dogs followed up to four years postoperatively. They fixed the lungs in situ in the same manner in both control and pneumonectomized animals then took sections of upper and lower lobes to represent more or less a complete cross-section. By counting the alveoli in microscopic fields of known diameter they were able to estimate the average diameter of an alveolus. In the controls, the normal alveolus of the puppies measured 116 and in the adult dogs 106 microns. Repeating this procedure on the remaining lung of pneumonectomized animals they found that there was a slight decrease in the diameter of the alveolus of puppies sacrificed at two, three and four years postoperatively, whereas there was an increase in the average diameter of the alveolus to 129 microns in the adult pneumonectomized dogs. In these same microscopical studies they observed distension of the atria and in places rupture of the alveolar septa with resultant fusion of the alveoli. This latter phenomenon was confined for the most part to the marginal areas of the remaining lung and was more apparent in the animal sacrificed at four years postoperatively than in those sacrificed at the earlier periods.

Elastic tissue studies, they stated, revealed in general in the three dogs which were pneumonectomized as puppies, a distribution of fibers much the same as in the controls but in a few places the fibers appeared perhaps slightly fragmented. On the other hand, in the adult series there was a clumping of elastic fibers in the thickened ends of ruptured alveolar septa and a suggestion of fragmentation in the walls of many of the intact alveoli. They again found this a more prominent feature in the dog sacrificed at four years postoperatively than in the earlier animals. They were careful to point out, however, that this evidence of fragmentation could 'only be considered as subjective, since objective demonstration was difficult to obtain'.

In interpreting their results these authors concluded that the small size of the alveoli in the remaining lung of pneumonectomized puppies indicated that hyperplasia must have occurred since each lung was almost twice the normal size. However, they also felt that there was a slight tendency in these hyperplastic lungs towards dilatation of atria and fusion of alveoli in the late postoperative period. On the other hand, in the adult pneumonectomized animals they concluded that there was no histological evidence of hyperplasia but rather there was merely a dilatation of the respiratory units with evidence of the development of chronic emphysema. This latter state they based upon the rupture of alveolar septa with thickening and clubbing of the ruptured ends, collapse of capillaries and the possible fragmentation of elastic tissue.

Some criticism of this study is warranted. Very definite conclusions are drawn from a study of only three pneumonectomized puppies and two pneumonectomized adult dogs, which is too small a series on which to base such conclusions. Furthermore, the evidence upon which they base a pathological diagnosis of chronic emphysema is sketchy, to say the least. Most other investigators, on more extensive studies, disagree with these authors. Furthermore they make no mention of possible hypertrophy of the remaining lung, yet they record that grossly the remaining lung is twice its normal size and attribute this enlargement to distension, for the most, of alveoli, while yet in actual measurements they record that in the adult the alveoli increase in size from 116 to 129 microns. This inconsistency requires explanation. Their histological studies are not reported in any detail. Thus one is justified in questioning their findings.

It is interesting to note that Adams (2) in discussing this paper at the time of its presentation, stated that the results of similar studies which he and his co-workers were at that time pursuing confirmed these findings in every alveolar septa with thickening and clubbing of the ruptured ends, collapse of capillaries and the possible fragmentation of elastic tissue.

Some criticism of this study is warranted. Very definite conclusions are drawn from a study of only three pneumonectomized puppies and two pneumonectomized adult dogs, which is too small a series on which to base such conclusions. Furthermore, the evidence upon which they base a pathological diagnosis of chronic emphysema is sketchy, to say the least. Most other investigators, on more extensive studies, disagree with these authors. Furthermore they make no mention of possible hypertrophy of the remaining lung, yet they record that grossly the remaining lung is twice its normal size and attribute this enlargement to distension, for the most, of alveoli, while yet in actual measurements they record that in the adult the alveoli increase in size from 116 to 129 microns. This inconsistency requires explanation. Their histological studies are not reported in any detail. Thus one is justified in questioning their findings.

It is interesting to note that Adams (2) in discussing this paper at the time of its presentation, stated that the results of similar studies which he and his co-workers were at that time pursuing confirmed these findings in every respect. One year later, when the results of his studies were reported in a paper by Rasmussen, Adams and Hrdina (68), he entirely reversed the opinions expressed previously in 1932 (3) and 1940 (2). This report was based upon a study of thirty-three adult dogs in which varying amounts of pulmonary tissue were either excised or destroyed. They stated that adult dogs could tolerate a reduction of functioning pulmonary tissue to fifteen percent of normal, or, in other words, could live a fairly normal existence when all but one lobe had been destroyed. On histological examination of the remaining functioning lung tissue, they found that there was marked distension of alveoli and bronchi but that the larger the bronchi, the less extreme was the degree of distension. Thus the greater the amount of lung tissue which had been destroyed, the greater was the distension of the remaining functioning tissue.

In the animals in which all but three lobes had been removed they found, in addition, a suggestion of diminution in the number of capillaries but although the fibrous and elastic tissue elements were somewhat stretched they were not disrupted. The one lobe dogs revealed the most extreme degree of changes. Besides the marked degree of distension, there was an actual rupture of the walls of some of the alveoli, especially those located in the vicinity of the pleura. The alveolar septa were stretched into thin avascular strands and thus giving rise to large non-functioning vesicles. The actual breakdown, they felt, occurred not primarily in the alveoli, but rather in the terminal respiratory units as a whole. They concluded that this did not, however, represent a true emphysema because the capillaries and elastic and fibrous elements were intact. They explained that the club-like structures, taken by Longacre and Johansmann to indicate emphysema, were, in reality, clumps of muscle cells and elastic and collagenous fibers of the walls of alveolar ducts situated between the air sacs and alveoli. They were emphatic that these changes in the remaining lung did not represent emphysema and one gathers that they felt that, following excision or destruction of lung tissue, the remaining functioning tissue simple becomes distended. They presented no evidence to suggest hypertrophy or hyperplasia.

It is apparent, from this foregoing review of the literature, that there is no unanimity of opinion as to the fate of the remaining lung following pneumonectomy. For the most part, all are in agreement that a true emphysema does not develop in the remaining lung. The controversy arises as to whether the remaining lung tissue undergoes hypertrophy or hyperplasia or whether it merely becomes distended. The problem in the growing animal, it is agreed, differs from that in the mature animal which is subjected to lung resection. It is the latter problem which we are attempting to elucidate by our present investigations.

Materials:

The lungs from the cats and dogs of the previous experiments, excluding those from the animals which died within two months postoperatively and those from animals which died from pneumonia, form the basis of this study.

Interest for the most part was centered upon the lungs of the animals surviving more than one year after operation. There were, all told, eight such animals -- seven cats and one dog. The lungs from four dogs sacrificed slightly more than two months after operation were also studied in order to discover any actual proliferative changes taking place within the remaining lung at the period when it had just recently reached its maximum degree of over-distension. Thus the lungs from a total of twelve animals were studied.

Methods:

The animals were all autopsied in the manner described in Chapter III. A careful gross examination was made of the remaining lung in situ. Following removal of the thoracic organs en masse, a cannula was inserted into the trachea and ten percent formalin in water was slowly run in until a pressure of twenty-five millimeters of mercury was reached. Thus the lung was completely distended under this pressure. The whole mass was then placed in a large container of the same solution, the cannula removed, and the lung permitted to collapse under its own elasticity. The lung excised at operation had previously been treated in the same manner.

Following fixation, sections were cut from both the upper and lower lobes as nearly as possible from the same locality in both excised and remaining lung. At least three, and sometimes more sections were taken from each lobe in order to obtain a representative picture of an entire cross-section.

The sections taken were then embedded in paraffin and histological preparations cut and stained. Three stains were used; hematoxylin and eosin, Masson's trichrome and Wiegert's elastic tissue.

A detailed microscopic study was then carried out. The sections from the remaining lung in each instant were compared with those from the excised lung of the same animal. Any significant changes were noted. Photomicrographs were taken to demonstrate some of the changes.

Results:

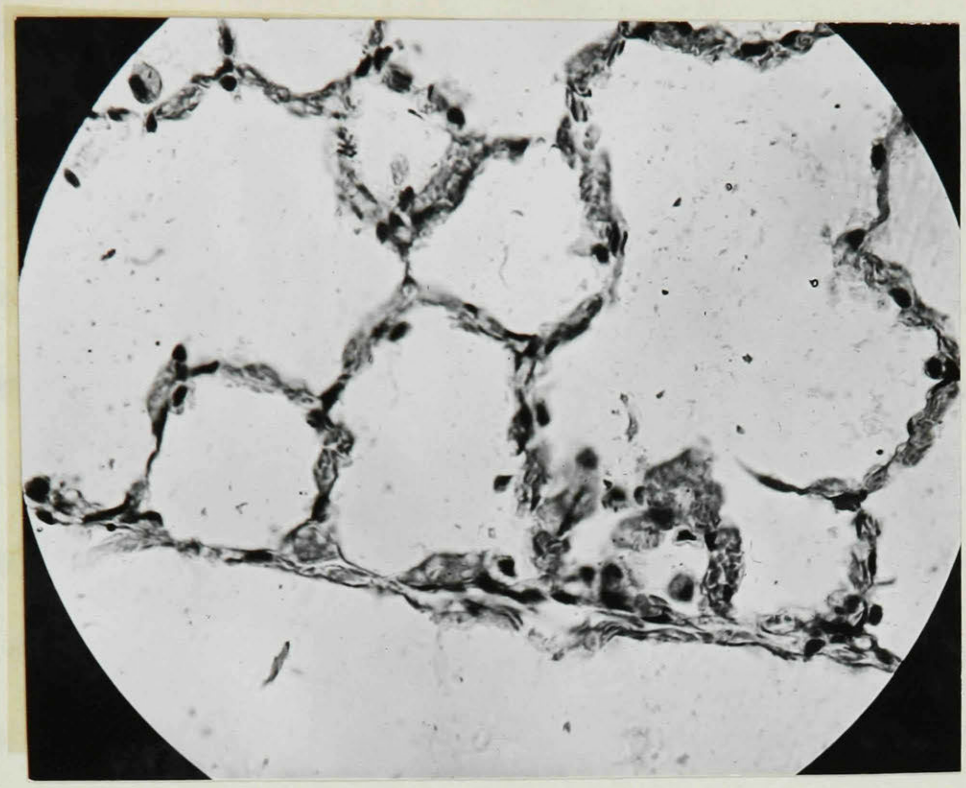
The lungs from all of the dogs autopsied approximately two months postoperatively revealed essentially the same gross and microscopical changes. Dog #15 is representative. This animal was sacrificed sixty-five days after a left pneumonectomy had been performed. The intrathoracic readjustments were essentially complete and therefore the remaining lung was almost twice its normal size in the expanded state in situ and herniated anteriorly and posteriorly through the mediastinum into the operated side. It was normal in color. No blebs or bullae were present, but along the margins one could make out distended air sacs. When the air was permitted to escape, the lung collapsed spontaneously to approximately the size expected in an equivalent normal. In the collapsed state it felt soft and crepitant and, as far as could be remembered, not unlike that removed at operation.

Under low power microscopical examination the pleura of the remaining lung was noticeably thicker than that of the excised. The alveoli were approximately the same size in both, but their walls appeared thicker and more congested. The bronchi and larger blood vessels of both were similar.

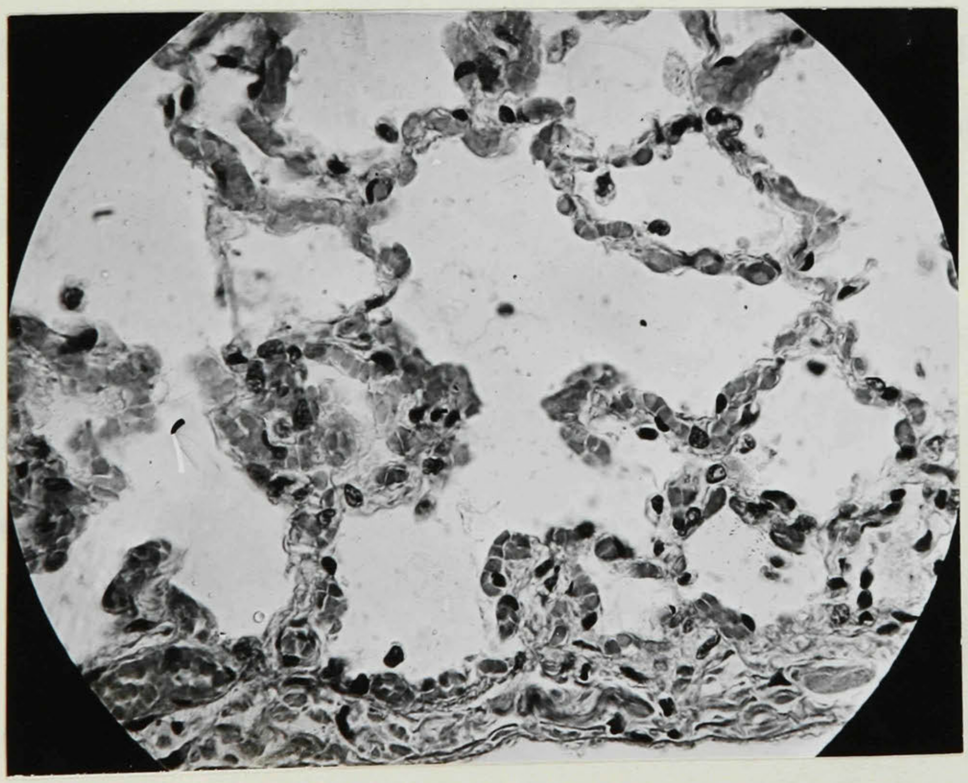
Under higher magnifications, some definite differences between the two lungs became apparent. Although the pleura of each lung varied in thickness in different locations, yet that of the remaining lung was on the whole thicker than that of the excised. This was due mainly to an increased amount of fibrous tissue elements and in part to elastic tissue (Fig. XVIII B). It seemed more cellular than the normal and many of the cells had large, ovoid, pale-staining nuclei and were identified as fibroblasts. Capillaries were slightly more prominent than in the normal. The elastic fibers were thicker and more numerous and did not appear fragmented.

The walls of the alveoli of the remaining lung appeared everywhere thicker and more cellular than in the normal. The thickening, for the most part, was due to a dilatation of the alveolar capillaries. The alveolar septa, particularly in the subpleural regions and in the vicinity of blood vessels, were more cellular than in the normal (Fig. XVIII B). For the most part, this cellular appearance was due to a prominence of the nuclei of the endothelial cells lining some of the capillaries. These nuclei were large, ovoid and lighter staining than normal. In addition, however, and independent of capillaries, were other cells scattered here and there and having an appearance not unlike the large cells lining some of the capillaries. Trichrome stains

Figure XVIII



A. Dog #15. Excised lung. 480X H. & E. stain



B. Dog #15. Remaining lung 65 days after operation.
480X. H. & E. stain.

Note: 1. Thickened pleura
2. Thickness and vascularity of alveolar septa
3. Cellularity of alveolar septa
4. Size of alveoli.

revealed possibly slightly more collagenous fibers in the alveolar walls of the remaining lung than in the excised. On the other hand, although the elastic fibers were distributed in the same manner in the alveoli as in the normal, they were definitely more numerous and thicker, particularly in the region of the atria and respiratory bronchioles. Nowhere was there evidence of fragmentation, nor for that matter was rupture of alveolar walls any more prominent here than in the excised lung and this appeared to be entirely due to technical faults in the preparation of the sections.

Numerous club-like structures could be seen in both lungs, but these were identified as merely isolated fragments of respiratory bronchioles and alveolar ducts separated by projecting atria and alveoli.

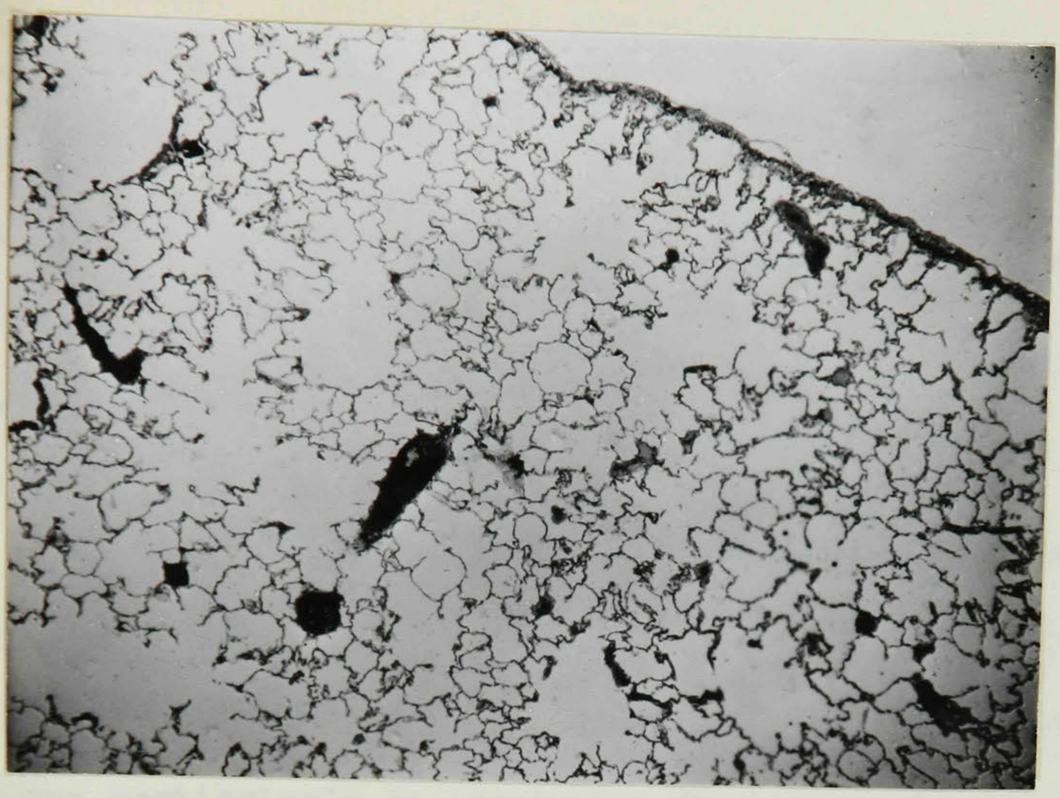
No obvious differences were noticed in the thickness or elements of the walls of bronchi and larger blood vessels of comparable size in the two lungs.

In summary, the four animals showed definite changes in the remaining lung as compared with the excised lung. The pleura was thicker in the remaining lung and this was due mainly to an increase in fibrous and elastic tissues. The alveoli were slightly larger and their walls thicker than in the normal. Some of this could be accounted for by a dilatation of the capillaries, but also to an increased cellularity and an increase in elastic and collagenous elements. The entire picture suggested a proliferative activity had taken place and was still taking place in the pleura and in the walls of the alveoli of the remaining lung. Nowhere was there any evidence to suggest emphysema.

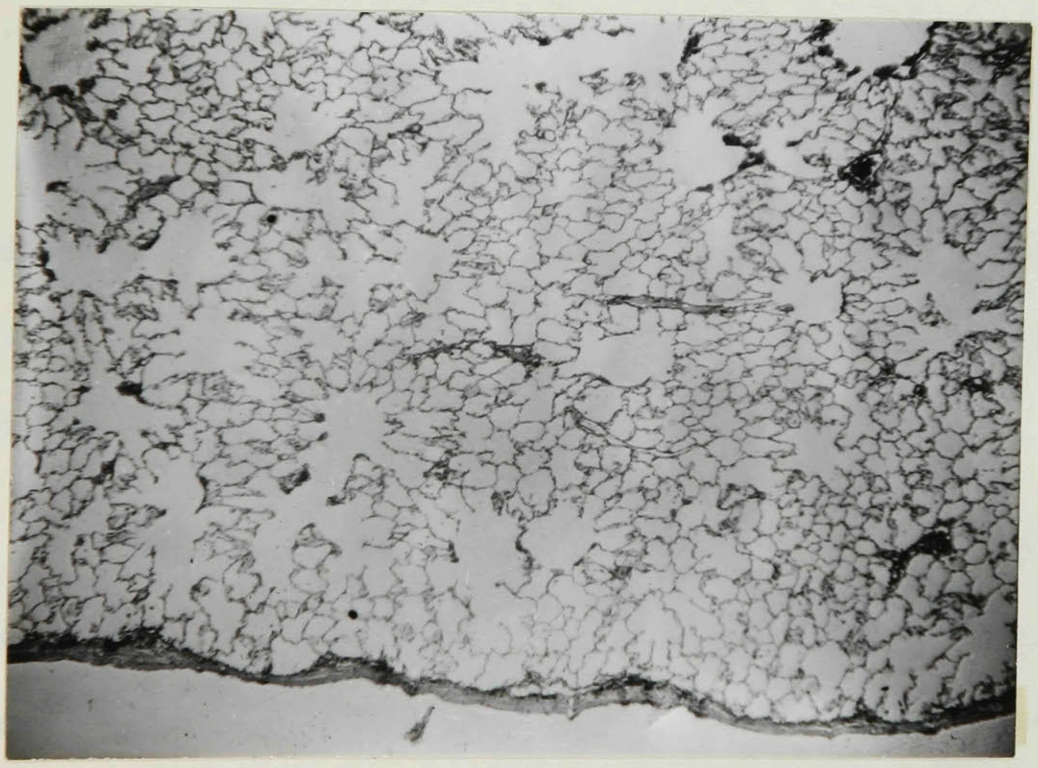
A study of the lungs of animals which survived operation for over one year was most interesting. Of these, the animal which had been pneumonectomized for the longest period was dog #20. It was operated upon on January 16, 1948 and sacrificed on June 1st, 1949, approximately one and one-half years later. For this reason it is described here in greater detail.

The gross findings at autopsy were essentially the same as those in dog #15. The lung collapsed spontaneously (Fig. XVI) and looked and felt entirely normal except that in the collapsed state it was slightly larger than would be expected of a normal lung from an animal of comparable size, or when compared with the collapsed excised lung, allowing for the normal differences in size. There were no blebs or bullae on the lung surface.

Figure XIX



A. Dog #20. Excised lung. 42X. H. & E. stain



B. Dog #20. Remaining lung 18 months after operation.
42X. H. & E. stain.

Note: 1. Thickened pleura.
2. Normal appearance of alveoli.

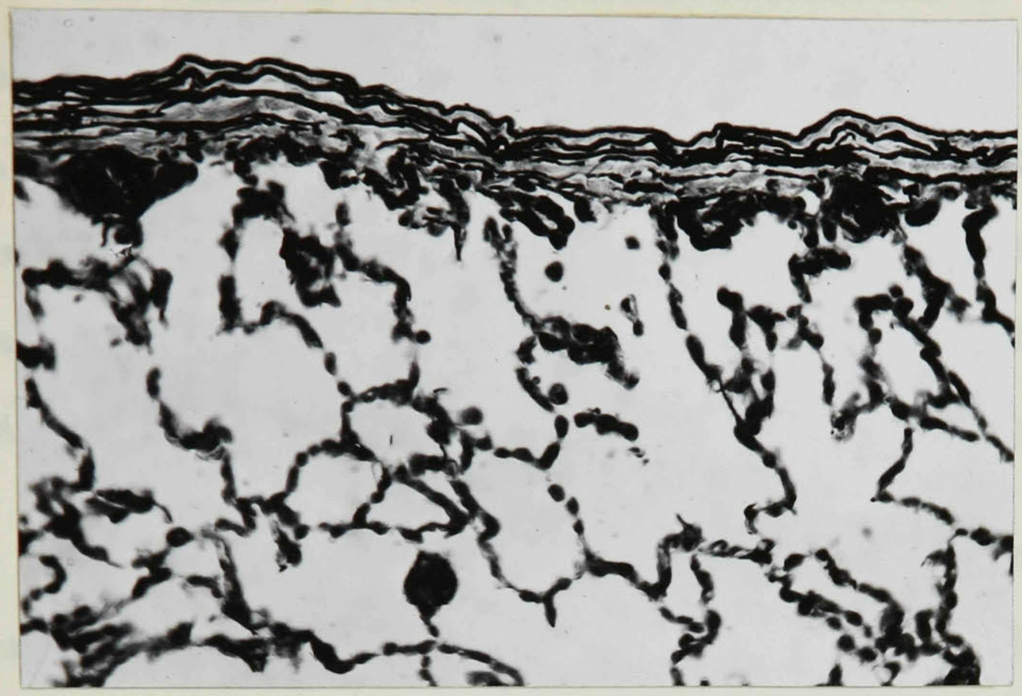
On microscopical examination under the low power objective there were a few obvious differences between the remaining lung and the excised. The pleura of the former was definitely thicker than that of the latter whereas the alveoli appeared entirely normal (Fig. XIX).

Under higher magnification this pleural thickening was due to an increase in the amount of elastic and fibrous tissues. The elastic fibers were increased both in number and more particularly in thickness (Fig. XX) and formed one or more organized layers.

The alveoli were essentially the same in diameter but their walls appeared slightly thicker than normal. The alveoli of both lungs were well vascularized, but those of the remaining lung were slightly more so for the capillaries appeared both larger and closer together.

Collagenous fibers were more prominent in the alveolar walls of the remaining lung and elastic tissue stains disclosed a fine, interlacing network of fibers standing out much more prominently than in the normal (Fig. XX). These fibers were both more numerous and thicker, particularly in the region of the atria and respiratory bronchioles and there was no evidence of rupture or fragmentation.

Figure XX



A. Dog #20. Excised lung. 320X. Elastic stain.

B. Dog #20. Remaining lung. 320X. Elastic stain.

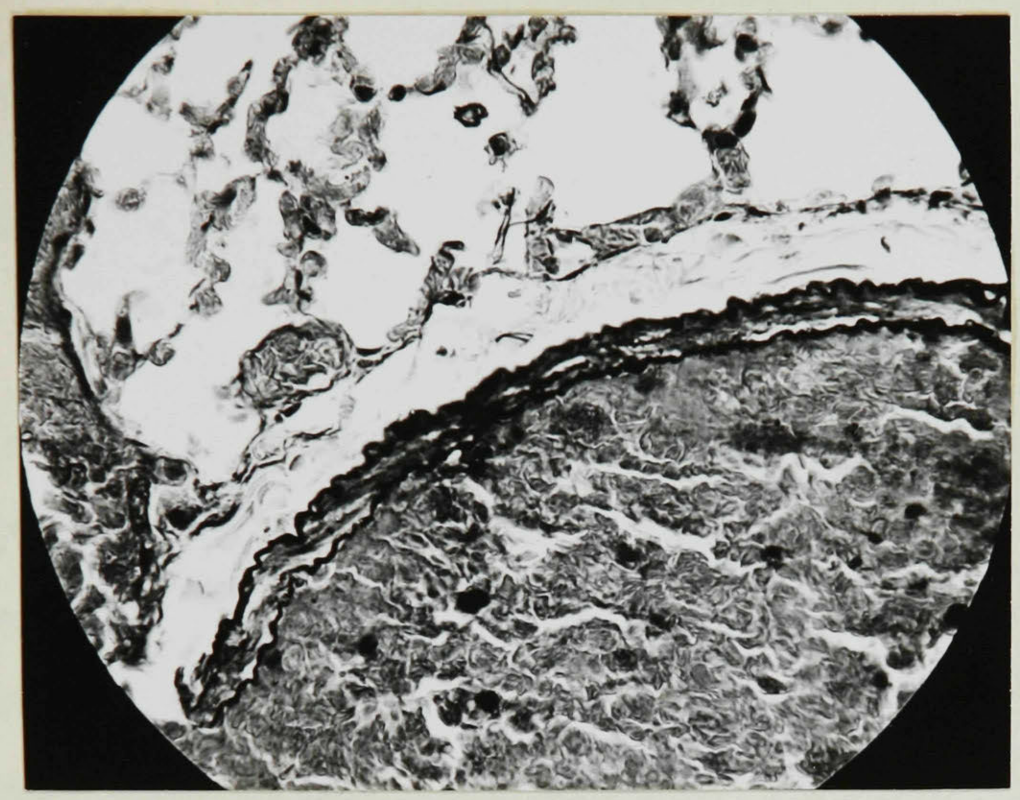
Note: 1. Thinnest area of pleura of B compared with thickest of A.
2. Thick, dense elastic layer of pleura of B.
3. Abundance of elastic fibers of alveolar septa of B.

The walls of the respiratory bronchioles of the remaining lung were slightly thicker than those of the excised. The increased thickness seemed almost entirely due to the muscle elements and not to an increase in collagenous or elastic tissue. The club-like knobs of bronchioles and alveolar ducts stood out more clearly in the remaining lung.

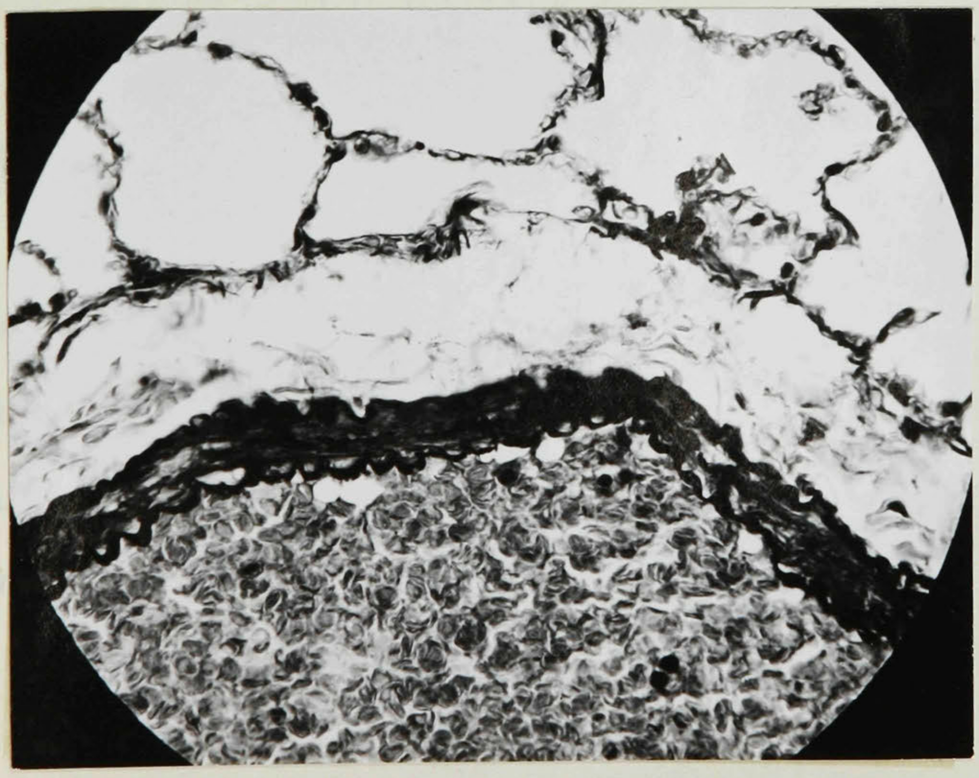
The smaller arteries of comparable diameter in the two lungs seemed to have slightly more and thicker elastic layers than in the excised (Fig. XXI). The larger arteries, however, were essentially the same in both. Similarly the larger bronchi of comparable diameters were apparently identical.

The gross and microscopical findings in the remaining lung of the seven cats which had survived for over one year after operation were essentially the same as in the dog but some of the features were not quite so marked. One very obvious difference was again the increased thickness of the pleura of the remaining lung with increased amounts of fibrous and elastic elements. The alveoli were not significantly increased in diameter but their walls seemed thicker than normal. The capillaries were closely packed together. The elastic fibers again were markedly increased, but the collagenous fibers although also increased did not constitute

Figure XXI



A. Dog #20. Small artery in excised lung.
480X. Elastic stain.



B. Dog #20. Small artery in remaining lung.
480X. Elastic stain.

Note: 1. Arteries of similar size compared.
2. Elastic layers are thicker in B.

so obvious a difference in the lungs as in the case of dog #20. The bronchiolar musculature was again slightly thicker than in the normal. There was no essential difference between comparable sized arteries and bronchi of both lungs.

The remaining lungs of the cats which survived operation for over one year, therefore displayed nearly all the features of that of the dog except that, excluding the pleura and elastic tissue elements, the changes were not quite so apparent. These lungs, likewise, had none of the characteristics of emphysema, nor was there any evidence to suggest that they suffered from the undue demands and strains placed upon them.

Discussion:

The difficulties in interpreting lung histology are fully appreciated and therefore one must exercise caution in formulating conclusions based upon rather minute histological changes. However there were some indisputable positive findings in this study.

In the first place the remaining lung in the expanded state was almost twice its normal inflated size (Figs. XIII and XV). It collapsed spontaneously (Figs. XIV and XVI). There were no blebs or bullae and although in the expanded state distended alveoli could with the naked eye be readily identified along the lung margins, in the collapsed state these were no longer apparent. This is indirect evidence then that the lung possessed well functioning elastic tissue. Certainly from the gross appearance it had none of the features of emphysema.

The histological studies revealed some definite changes. There was a very apparent increase in thickness of the pleura and it was clearly due to an increased amount of elastic and fibrous tissue. The elastic fibers were not only more numerous but on the whole thicker and in no way disorganized. The alveoli were not ballooned out or ruptured. On a cursory examination one would say that the lung was entirely normal. Although the alveoli may have seemed a little larger in diameter in some sections one cannot say that this could not have been due to the method of fixation. However, the alveolar walls, on the whole, were thicker than normal. They were every bit as well vascularized as those of the excised lung. In fact, the capillaries themselves seemed slightly larger and more closely packed together than in the normal. There was a very obvious increase in the elastic framework of the alveoli so that they appeared to possess almost twice as much elastic tissue as the normal.

The fibers, besides being more numerous were thicker. There was no evidence of fragmentation. There was also a definite increase in the amount of collagen in the alveolar walls. The remaining lung was therefore strengthened through an increased amount of elastic and fibrous tissue of both the pleura and alveoli and the vascularity, if anything, was increased.

The gross and histological appearance of the remaining lung clearly deny the presence of emphysema. This observation is in agreement with the majority of the reports in the literature. Only Longacre and Johansmann (51) maintain that emphysema occurs in the remaining lung. The evidence which they present in support of their conclusions is inadequate. In the first place only two adult dogs were studied. In the remaining lung they stated that alveoli were ruptured but that this was confined for the most part to the marginal areas. They also reported a clumping of elastic fibers in the thickened ends of ruptured alveolar septa and a suggestion of fragmentation of fibers in the alveolar walls. The latter they pointed out could only be considered subjective, since objective demonstration was difficult.

Ruptured alveoli may be found in many essentially normal lungs and therefore cannot be considered as evidence, per se, of emphysema. As Adams (68) has pointed out, the club-like structures which were taken by Longacre and Johansmann as an indication of emphysema were, in reality, clumps of muscle cells, elastic and collagenous fibers of the walls of alveolar ducts situated between air sacs and alveoli. We also observed these structures in both the excised and remaining lungs and it is very obvious that Adams' interpretation is correct. In the remaining lung, as a matter of fact, they stood out more prominently and this appeared due to mainly an increase in the amount of muscle tissue within them. They themselves admitted that the fragmentation of elastic tissue was questionable. It would therefore seem from the gross and histological studies of the remaining lung that there is no proof that emphysema develops.

In recent years, in certain centers in the United States, it is felt that patients who have undergone pneumonectomy in time develop emphysema directly as a result of the over-distension of the remaining lung. Thus Cournand and associates strongly advocate an extensive thoracoplasty in order to reduce the size of the space created by the excision of one lung, for they say that this 'not only does not impair ventilation but often improves it by reducing the degree of pulmonary distension'. This recommendation was made on the basis of pulmonary function studies (18). He felt that this also applied to children yet in a recent report (19) of a study of four young subjects who had been operated upon four to six years previously, he stated that 'in two patients who had developed a moderate degree of pulmonary distension, the only significant findings were a reduction in breathing reserve from normal and a marked degree of oxygen unsaturation in the arterial blood brought out by a very strenuous type of exercise.' On a moderate degree of exercise these same patients, he stated, showed no significant changes from the normal controls. Furthermore, on measuring the pulmonary blood pressures he found no significant degree of elevation.

There are others, who from similar investigations, are not in agreement with Cournand's conclusions. Ornstein (62), for example, has stated that 'one interesting thing we have learned, particularly in pneumonectomies, is that a thoracoplasty following pneumonectomy cuts down on ventilation markedly'. He is of the opinion, based upon his pulmonary function studies, that the remaining lung may hypertrophy and not become emphysematous. Therefore he feels that it is wiser to allow the lung to fill the whole thorax rather than restrict it by a thoracoplasty. Wright (94) would seem to share this view.

There are still others, more cautious, who feel that from studies of pulmonary function in pneumonectomized humans, emphysema probably develops but that it remains within moderate limits and does not encroach upon function to any degree (12). They would seem to use the term 'emphysema' rather loosely here.

Pulmonary function studies in pneumonectomized dogs have been reported. Drastich, Adams, Hastings and Compere (24) in a study of eleven pneumonectomized animals up to fourteen months after operation, found that measured amounts of moderate exercise affected the animals no more than it did the controls. It was only after severe exhausting exercise that the pneumonectomized animals showed more fixed acid in the blood. This they interpreted as probably indicating that the tissues were receiving less oxygen than normal.

Longacre, Carter and Quill (5), from somewhat similar studies, concluded that the cardiopulmonary reserve following pneumonectomy is sufficient for resting conditions and moderate exercise but that as the strain is increased the impairment of reserve becomes more apparent. They noted, after the initial fall, a gradual improvement in function over succeeding months. They felt, therefore, that this was due to compensatory changes, which they were unable to explain unless on the basis of hypertrophy or hyperplasia of the remaining lung.

A few years later, Longacre and Johansmann (51) reported a further follow-up of these experiments and stated that although within the first year postoperatively the animals showed a regain of function to seventy to eighty percent of the preoperative level, over the ensuing three years the amount of compensatory return of function was gradually lost in varying degree in different animals. It was maximum in the animals pneumonectomized after they were full grown and only minimal in those pneumonectomized as puppies.

Phillips, Adams and Hrdina (65) in a study of the physiological adjustments in adult dogs following ablation of one lung, found that little or no disturbance in cardio-pulmonary function ensued.

There is, therefore, from histological and pulmonary function studies on the pneumonectomized human and dog no indisputable evidence that emphysema develops in the remaining lung.

It is admitted by all, that following excision of one lung in the animal, the remaining lung, at least initially, becomes over-distended. From here opinions differ, As previously mentioned, there are those who contend that the lung becomes emphysematous. There is another group, lead by Rienhoff, who maintain that the sole response of the remaining lung is one of simple over-distension. This opinion he formulated upon a study of pneumonectomized adult dogs (72) and humans (69, 70). He coined the term 'compensatory dilatation' of the remaining lung because he felt that this dilatation was a response to increased physiological demands. As a result of his studies he therefore advised against interfering with this response by means of procedures which would reduce the size of the thoracic cavity. Adams and coworkers (68) and Bremer (17) agree, for the most part, with Rienhoff. Others, however, as mentioned, agree that the immediate response is one of over-distension but that it is not compensatory but on the contrary is decompensatory for it results in diminished cardiopulmonary function and may even result in true emphysema.

Those who believe that there is a 'compensatory dilatation' of the remaining lung base their conclusions upon the absence of histological changes, other than over-distension, and functional studies. We disagree because we have seen definite microscopical changes in the remaining lung.

There are therefore others who, agreeing that the initial response of the remaining lung is one of simple over-distension and that it may always be somewhat so, maintain that definite proliferative changes take place in the adult lung in response to increased demands or strains. The response, then, must be one of hyperplasia or hypertrophy.

In considering hyperplasia to be the response it is essential to discuss the adult and growing animals separately. In regard to adult pneumonectomized dogs, no investigators have produced any proof that there is a hyperplasia of the remaining lung. On the contrary, Rienhoff, Reichert and Heuer (72), by counting the bronchial branchings to the terminal air sacs in comparable segments of control and remaining lungs found no numerical differences between the two. This they cited as proof that hyperplasia does not occur. It would seem to be indisputable proof for as Bremer (16) and others have shown, lungs grow through a continuous budding of bronchi. Furthermore, no one has observed any budding of new alveoli, as has been described by Bremer in the lungs of normal growing animals.

As mentioned earlier in this chapter hyperplasia has been described in the remaining lung of pneumonectomized adult rats by Hilber (41). Bremer (17) has discussed this and quoted Donaldson's extensive studies of the rat and of others of the guinea pig. It has been demonstrated clearly that in animals of this family the growth factor is present late on into adult life, for it is present up to three years after sexual maturity. This then might well explain some of the conflicting reports in the literature on the fate of the remaining lung in adult animals when rabbits, rats, dogs and cats have been used as the experimental material.

It would seem then, that so far as the adult pneumonectomized dog, cat and probably man are concerned, compensatory overgrowth, in other words hyperplasia, does not take place in the remaining lung. On the other hand, there is some fairly conclusive evidence that this might be the case in the animals pneumonectomized during their growth period. Indisputable proof is still awaited in the case of the pneumonectomized child.

There remains to be considered the question as to whether or not there is hypertrophy of the remaining lung of the animal pneumonectomized after growth has ceased. We believe that there is. Eliminating the rodents from this discussion, there is considerable support for this contention. Kawamura (44), employing adult dogs, has described the histological process of this hypertrophy in more detail than any other investigator. Behrend and Mann (7), although concluding that 'hypertrophy, hyperplasia, emphysema or even simple dilatation is not generally apparent in the alveoli of the single lung remaining' described some definite proliferative changes in the alveolar walls. They recorded that in the earlier postoperative periods there were focal areas of proliferating histiocytes which resulted in a symmetrical thickening of these structures over the normal. Amongst these cells were intertwining proliferating capillaries, which they felt increased to a considerable degree the blood supply of the lung. As the postoperative period lengthened, they said that these histiocytes gradually became transformed into fibrocytes so that there was eventually an increased amount of fibrous tissue in the walls. With this there also developed a very marked increase in the reticular framework.

This histological description closely parallels that of Kawamura. The differences would seem to lie mainly in the interpretations. Both observed capillary proliferation in the alveoli but the former considered the large, pale-staining cells as histiocytes and that capillaries grew in amongst them, while the latter considered them as proliferating fibroblasts and capillary endothelial buds. We also saw these cells in the sections taken from the remaining lungs of animals sacrificed approximately two months postoperatively and experienced the same difficulties in interpretation. Both agreed that there was an increased vascularity and increased amount of collagenous tissue. Behrend and Mann reported a marked increase in the reticular framework. Kawamura reported that the elastic framework was greatly increased. In the alveolar walls of the remaining lung of our animals, the most striking feature was a tremendous increase in the amount of elastic tissue over that in the excised lungs.

We are convinced that both were describing the same histological changes, but that the differences are purely a matter of their interpretations. We also observed these changes and experienced the same difficulty in interpreting the nature of the cells. Like Kawamura, we found the elastic fibers of the alveolar walls exceedingly more numerous and thicker than in the normal. In addition, like Kawamura, we found the pleura strikingly thickened and containing more collagenous and elastic tissue than normal. This activity in the remaining lung of pneumonectomized adult cats and dogs undoubtedly results in a strengthening of the organ and to some increase in its size. This response to the excision of one lung, according to definition is 'hypertrophy'.

We are quite prepared to admit that it is quite possible that the remaining lung, although it hypertrophies, may yet with the passage of time display a gradual loss of function. The remaining lung, despite the degree of hypertrophy, is still greatly over-distended. This could conceivably in time be injurious, but there is as yet no indisputable evidence that this is so. Pulmonary function tests would seem to suggest that such is the case but any loss of function appears too slight to be of significance.

It would seem probably that this response of the remaining lung is due, at least in part, to the degree of mechanical over-distension to which it is subjected. It could, in part, be a response to the shifting of the whole circulation through the one lung and the increased demands placed upon it. The answer to this might be obtained by a study of the remaining lung of pneumonectomized animals in which over-distension has been prevented through some means or other.

<u>Summary</u>:

Definitions of the terms employed in this study have been given and the literature then reviewed and interpreted, where necessary, in this light.

The materials and methods in the present investigations have been described. It has been carefully pointed out that the problem under consideration concerns only fully grown animals, so that, as far as it was possible to determine, only such animals were employed.

Gross and histological examinations of the remaining lung were compared with those of the excised and variations recorded and described in detail. Photomicrographs of both lungs have been included to demonstrate some of the points mentioned in the text.

It has been stressed that very definite differences existed between the excised and the remaining lungs. One striking feature was a thickening of the pleura due to an increased amount of collagenous and elastic elements. A similar state existed in the walls of alveoli but, in addition here, there was also a definite increase in the vascularity. Other less significant changes have been described as well, but because interpretation is necessarily difficult they have not been stressed.

The various opinions as to the fate of the remaining lung have been discussed and evaluated in the light of all the available information. From this it was found that no indisputable proof exists that the remaining lung becomes emphysematous. Similarly, although the remaining lung is over-distended, evidence is against this being the sole response to the excision of its mate.

The question of hyperplasia of the remaining lung has been considered and it has been shown that there is no proof that this develops in the remaining lung of pneumonectomized adult dogs, but that it may occur in immature animals and in adults of the rodent family. Such, it has been pointed out, might well explain some of the confusion that exists in the literature.

Finally hypertrophy of the remaining lung has been discussed and the evidence presented as proof that such actually takes place in adult cats and dogs. Whether or not this is a response to over-distension or to increased physiological demands placed upon the lung has yet to be determined.

Conclusions:

1. The remaining lung of pneumonectomized adult dogs and cats becomes hypertrophied. Although a large part of the enlargement is due to over-distension, some is also due to a marked increase in thickness and amount of elastic and collagenous fibers of pleura and alveolar walls and to an increased vascularity of the alveoli. The organ is therefore enlarged and strengthened through the increase in these normal elements, or, in other words, it is hypertrophied.

2. There is no evidence that the enlargement of the remaining lung in adult dogs and cats is due to hyperplasia.

It is possible that this might, in part, be the case in rodents and immature animals.

3. There is no proof that the strain placed upon the remaining lung is injurious to it and that emphysema eventually develops.

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M.Sc. EXPERIMENTAL SURGERY

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PROBLEMS ASSOCIATED WITH THE OPERATION OF PNEUMONECTOMY

The story of the development of the operation of pneumonectomy has been briefly told. In this some still unsolved problems associated with the operation appear. One of these is the obtaining of permanent closure of the sectioned bronchus. A study has been made of the bronchial stump and the reasons behind the method recommended to ensure permanent closure presented.

There has been some controversy regarding the anatomical readjustments within the thorax following pneumonectomy. These have been described in the dog, rabbit and cat and the problem enlightened.

A study has been made of the fate of the remaining lung in pneumonectomized full grown cats and dogs sacrificed up to eighteen months after operation. The remaining lung was not found to be emphysematous, but hypertrophied. A striking feature was a tremendous increase in the elastic fibers of the pleura and alveolar septa.