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I hereby recommend that the thesis prepared under my supervision by J. J. Longacre, M. D.

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A STUDY OF THE TECHNIQUE OF AND THE PHYSIOLOGIC CHANGES FOLLOWING EXPERIMENTAL TOTAL PNEUMONECTOMY

A dissertation submitted to the

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by

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I N D E X

I. Experimental Total Pneumonectomy with Reference to the Care of the Bronchial Stump.

A. Historical Review

Although thoracic surgery has made great progress in recent years, it is not a new field. Records of thoracotomy for empyema along with recognition and drainage of pulmonary abscess can be traced back to the writings of Hippocrates in 400 B. C. Hippocrates - On Diseases (Littré, Book II, Vol. 7, pp 93).

"When an abscess forms in the chest there is a dry cough, pain and fever. There is a sensation of weight in the pleura, and a sharp pain always in the same place, severe thirst, warm drinks are regurgitated and the patient cannot lie on the painful side, but is able to lie on the unaffected side, but when he lies down he feels as if a stone were hung from him. The side swells and reddens and the feet also swell. This requires incision or cautery, then let the pus run out till the tenth day and plug with raw flax. When the tenth day comes, inject warm wine and oil, so that the cavity may not at once become dry, and stuff with linen. Let out the injected fluid and reinject. Do this four days running. When the fluid becomes as thin as strained barley broth, and small in amount, and sticky to the touch, put in a tin tube, and when the cavity is quite dry cut off a little of the tube and continue until the cavity contracts gradually down on it."

The subject seems to have been either avoided or neglected until the end of the sixteenth century when Schenk in 1584 called attention to this important branch of surgery. John Bell in 1807, far in advance of his time, described clearly and accurately the symptoms, signs, and prognosis of wounds of the pleura, lung, and heart. In 1878, Grinnell* reported the

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* "Some Caddoe boys were practicing with bows and arrows, when one about eight years of age received a shot in the lower portion of the thorax, between the fifth and sixth ribs, just to the left of the median line.

"The barbed arrowhead entered deeply into the lung.

"The boy immediately grasped the shaft and drew out the arrow-successful removal of a considerable portion of the lower left lung, which had been pulled through the chest wound in the attempts on the part of the patient, an Indian, to extract a barbed arrow. Although considerable suppuration followed, the patient finally recovered.

The earliest experimental work on resection of the lung was reported by Gluck[2] in 1881 when he removed the entire lung on one side from 6 dogs and 14 rabbits. With the exception of 2 rabbits, all died in from seven to ten days. Marcus'[3] and Block's[4] experiments performed in the same year were equally discouraging. Biondi[5] (1882) reported his results, which were the best obtained in these early investigations. Of 11 pneumonectomies, only 4 patients died of septic pleuritis. Zakharevitch's[6] (1890) results equalled Biondi's. In 1891, Willard[7] performed a successful pneumonectomy in a dog by suturing the stump which he had ligated en masse into the wound.

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the head carrying with it, through the orifice, quite a large portion of the lung, not, however, severing it from the remainder of the organ. The family lived some fifteen miles from my office; and the'medicine man' near at hand who was summoned, was unable by his blowing, howlings, or enchantments to make the lung replace itself or to remove it. He decided that the part thus drawn out was 'fat,' and that was as far as he could go.

"I did not see the case until twenty-four hours after the injury was received. When seen the exposed lung was congested, so that it resembled the liver or spleen, more than lung tissue. The weather was exceedingly warm and the odor was already becoming offensive.

"Chloroform was at once administered, and after placing a ligature around the part close to the wound, I removed the portion of the lung exposed to view. Then washing the portion below the ligature which still tended to protrude--with a solution of per chloride of iron--I returned it within the small

Murphy[8] (1898) lost 8 out of 9 dogs with septic pleuritis. In 1906, Green[9] resected parts of lungs in 14 dogs, losing 7 of pleuritis. The following year Tiegel and Mitt[10] called attention to the fact that ligation en masse was a primitive method. They advised loose mass ligation with silk about the hilum, followed by peripheral ligation of the vessels. Following resection, the bronchial stump was cauterized with heat and ligated distal to the first ligature. His method also was followed by the complications of hemorrhage and bronchial fistula. Frederich[11] (1908) advised separate ligation of vessels. Following resection of the lung he removed the mucous membrane, after which the bronchus was ligated to bring the raw surfaces into apposition. Danielson[12] (1908) concluded that it was possible to close the main bronchus with silk. In the same year Halsted[13] reported 21 thoracotomies with only one subsequent infection in the pleura.

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opening made by the arrow, and applied sutures.

"The portion of lung thus removed was 4-1/2 inches in length and 2-3/4 inches in breadth at the widest part.

"Some degree of suppuration took place a few days after, and two weeks after the operation the ligature came away with a quantity of pus. Since that time the boy has steadily improved. He has now quite recovered, and is resuming his usual sports."

In this respect his results were quite different from those of earlier investigators. He advised bisecting the bronchus and removing the mucous membrane, followed by suturing of the flattened halves of the bronchus with through-and-through silk sutures together with a series of sutures placed around the edges. Willy Meyer[14] (1908) described his inversion method in which the bronchial mucosa was undisturbed and the closure of the bronchial lumen accomplished at the expense of the peribronchial tissues. In 21 dogs he crushed the main bronchus and ligated it with a transfixion suture of medium silk. Of these 21 dogs he lost 4, a mortality of 19 per cent. Robinson and Sauerbruch[15] removed one lung from each of 38 animals with only 4 recoveries, using ligation en masse. Schlesinger's[16] results (1911) were similarly poor. Quinby and Morse[17] concluded that the method as described by Meyer seemed the most accurate and successful after treating each bronchus separately in 38 dogs with only 8 deaths.

Garré[18] (1912) advocated the sewing of the lung over the opened bronchus, after having placed a ligature about the bronchus. Henschen[19] (1914) suggested the introduction of a plug of fascia into the bronchus and closing the stump over it. Giertz[20] undertook the problem but modified it by using silk mattress sutures to close the bronchial stump; following which he covered it with small fascial transplants sutured with silk to the peribronchial tissues. Of 10 dogs operated upon, he lost 2 of tension pneumothorax. Kawamura[21] (1914) modified the method of Tiegel by using a proximal bronchial ligature. Only two bronchial fistulas resulted in the 23 pneumonectomies performed on dogs.

Heuer and Dunn[22] (1920) employed all the previous methods described along with several new ones with 13 recoveries in 23 pneumonectomies. Feiermann[23] (1925) after reviewing the various technics of treatment of the bronchial stump considers the method as described by Willy Meyer the best, but suggests the use of a reverse purse-string suture to the peribronchial tissues to give the stump a greater solidity. Bettman and his coworkers[24] (1928) reported an excessively high mortality in both lobectomies and pneumonectomies, losing 25 out of 27 dogs, and concluded that the closure of the bronchus was difficult on account of the "inherent inertness" of the bronchial wall tissues. Joannides[25] (1928) found that primary bronchi are hard to invert and that the results are bad. He consequently advised amputation of the lobe to be done through the lung tissue. All his dogs, however, showed evidences of pleural irritation with greater or lesser amount of exudation. Furthermore, at autopsy the site of suture was found always to be adherent to the thoracic wall. Schleuter and Weidlein[26] (1928), believing the invagination method as proposed by Willy Meyer to be the most ideal procedure for lobectomy, modified it by cutting the primary or secondary bronchus between ligatures, then inverting it with a No. L chromic catgut purse-string suture and in the case of a primary bronchus reinforcing it by three mattress sutures of silk. Following this, a final purse-string suture was placed to cover the mattress sutures with the looser peribronchial tissues. In 13 lobectomies on dogs in which this method was employed, 1 died of empyema, 1 of bronchopneumonia, 1 of distemper, and 1 of a cause unknown. In 4 pneumonectomies performed by treating each bronchus separately, one died of empyema on the fourth day. Nisson[27, 28] (1931) in the attempt to minimize the dangers of the complications following ligature en masse devised a two-stage procedure; surrounding the lobe to be excised with a coarse silk mesh bag to obliterate the pleural cavity, followed by resection and ligature en masse two to four weeks later. Adams[29] (1931), in order to reduce the dangers of bronchial fistula, applied 35 per cent silver nitrate to the bronchial lumen to produce bronchial stenosis prior to resection of the lung. Bryce[30] (1934) suggests a three-stage procedure: (1) the production of adhesions by a large mesh bag (Nisson); (2) the ligation of the pedicle of the lung followed by (3) the removal of the necrotic lobes. Sixty-six and sixtenths per cent of his animals (cats) survived this procedure.

Review of the literature not only of experimental lobectomy and pneumonectomy but also of the clinical fields (Hale,[31] Grinnell,[1] Duvon,[32] Morrison,[33] Robinson,[34-36] Lilienthal,[37-39] Sauerbruch and Robinson,[40] Graham,[41,42] Hinz,[43] Churchill,[44] Alexander,[45] Edwards,[46] Brunn,[47,48] Shenstone and Janes,[49] Eloesser,[50] Rienhoff,[51] Roberts and Nelson,[52] Heuer[53]) reveals that while hemostasis is the least troublesome factor, the obtaining of a completely air-tight bronchial stump is the most difficult as well as most important phase of the problem. The high incidence of bronchial fistula along with the high incidence of pleural infection are to be ascribed essentially to the inherent difficulties in the care of the bronchial stump. It is the "bête noire" of thoracic surgery. Sauerbruch very sagaciously summarized the problem, "Bei Lungen-amputation muss der grösste Wert auf eine zuverlassige Versorgung des Bronchialstumpfes gelegt werden. Sei ist ein technisches problem, das noch nicht vollstandig gelöst ist."

The inherent difficulties are to be explained on the basis of the singular anatomic construction of the bronchus. The bronchus is composed mainly of cartilage, which is prone to undergo degenerative changes when subjected to trauma. The poor blood supply, derived from the bronchial arteries, increases the inherent tendency of the cartilage to degenerate. In addition, the position of the cartilaginous rings continually tends to separate the opposed bronchial walls. It has been shown by Bettman and his coworkers[24] that the healing of a bronchial stump is brought about by the peribronchial tissues, which are also supplied by the bronchial arteries. Any interference with the meager blood supply of these structures by rough or careless handling of the stump will lead either to a failure of the peribronchial tissues to participate in the process of repair or to necrosis of the tissues with the inevitable development of a bronchial fistula. In analyzing earlier experimental work it will be noted that the stripping from the bronchus of the peribronchial tissues has been an important factor in the failures of many investigators.

The fact, also, that the healing is brought about only by the peribronchial tissues, the blood supply of which is meager, indicates very clearly that the reparative process must needs be slow and that a considerable time must elapse before the closure of the bronchial stump may be regarded as solid. Added to this, the fact that the mucous membrane of the bronchial tree is frequently contaminated with buccal organisms requires that no suture used penetrate into the bronchial lumen. The suture hole will act as a tract along which the bacteria may grow, giving rise to an infection not only of the bronchial stump but also of the pleura.

It would appear, therefore, that the most ideal operative technic for the treatment of the bronchial stump will be that method in which meticulous care is taken not only to prevent infection but also to avoid disturbing the normal continuity of the structures at the hilum, along with the minimizing of trauma to the bronchus.

The technic as described and executed by Willy Meyer meets essentially most of these requirements with the following exceptions: (1) the devitalization of bronchial tissue by means of a crushing clamp; (2) the difficulty encountered in bringing together the edges of the invaginated border without piercing through the wall into the bronchial lumen with the sutures; (3) the necessity for turning in an excess amount of bronchial wall the blood supply to which is interfered with by the acute angulation; (4) the difficulty encountered in attempting to invert a main bronchus of large dimensions by this method.

In the attempt to overcome the above disadvantages certain modifications were made and the following technic was executed in 30 dogs.

Technic.--Preoperative Medication: Morphine 1/4 gr. thirty minutes before operation. Anesthesia: Intratracheal ether using an Erlanger positive pressure apparatus with oxygen attachment.

The thorax is shaved on one side from the dorsal spine to sternum and from the second to the twelfth ribs inclusive. The skin is prepared by thorough scrubbing with soap and water followed by benzene, alcohol, and ether. The skin is then painted with iodine and the excess removed with alcohol followed by ether. A long linear incision is made just through the epidermis in the fifth intercostal space, extending it from the posterior axillary line forward practically to the sternum. This knife is now discarded and skin towels are immediately sutured to the skin edges. The incision is then carried through the subcutaneous tissues and muscle layers down to the endothoracic fascia with a second knife. All bleeding points are clamped and ligated. The pleura is then incised keeping close to the upper border of the sixth rib to

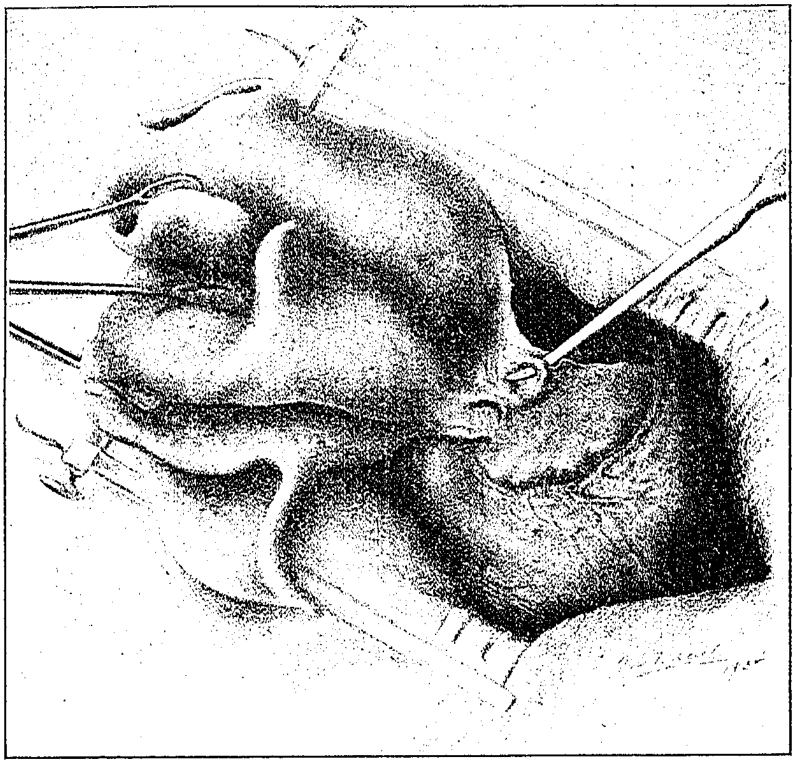

Fig. 1.--The pulmonary ligament has been incised up to the pulmonary vein. The vein is now isolated from between the two pleural reflections.

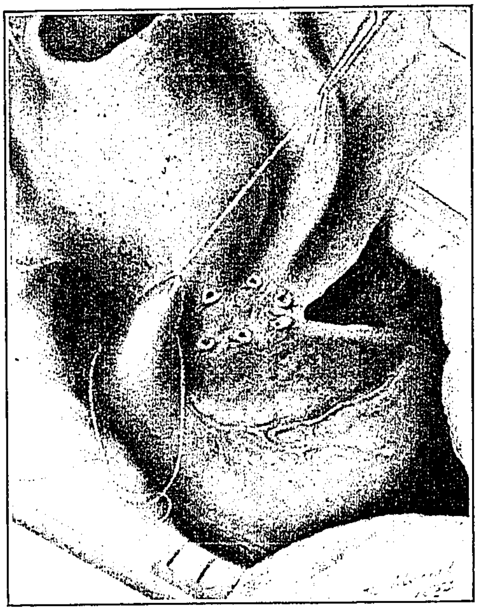

Fig. 2.—The pulmonary veins are isolated and divided individually between medium silk ligatures. The pulmonary artery is then isolated and doubly ligated with braided silk. This procedure completely frees the bronchus anteriorly, but does not disturb the peribronchial tissues.

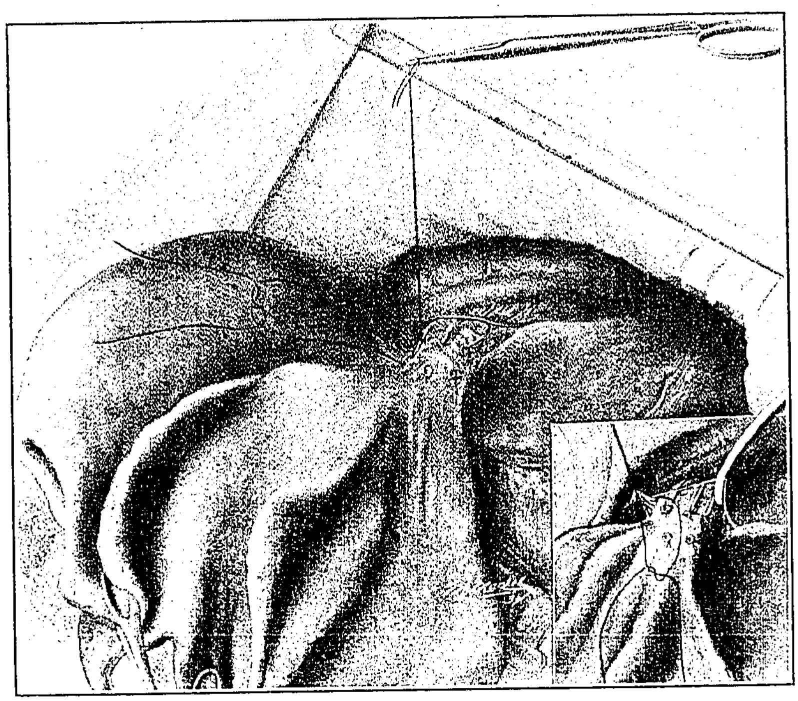

Fig. 3.—The technic for freeing the bronchus posteriorly. Note particularly the ligation of the bronchial vessels along the line of proposed trans-section of the bronchus. This technical detail is necessary to preserve an adequate blood supply to the bronchus and to the peribronchial tissues.

Insert shows the retraction of the vagus nerve (after division of its connecting fibers to the pulmonary plexus) so as to allow for a more adequate inversion of the bronchus without interfering with the vagus nerve.

avoid the intercostal neurovascular bundle. A wide exposure is obtained by the lateral flexion of the vertebral column with the convexity toward the operative side (by means of a folded sheet) along with the use of a laminectomy retractor. By grasping the individual lobes of the lung with sponge forceps and applying greater traction on the lower lobe, the pulmonary ligament is exposed to view. This is incised close to the pulmonary border up to the lowest pulmonary vein. At this point the vein is isolated from between the two pleural layers, and divided between medium silk sutures. The same procedure is carried out for the middle and superior pulmonary veins. The pulmonary artery is then isolated and ligated proximally with a ligature of doubled braided silk. A tie is then placed distal to this ligature, and the artery is divided between the two sets of ligatures.

This procedure now frees the bronchus anteriorly but does not disturb the peribronchial tissues. The lobes of the lung are now drawn toward the operator, thus exposing the posterior aspect of the root of the lung. Meticulous care at this point is necessary to preserve the blood supply to the bronchial stump and to prevent injuring the vagus nerve. Each of the two or three bronchial arteris (accompanied by their corresponding bronchial veins) is then isolated individually, doubly ligated with fine silk, and divided at the point at which the bronchus is to be cut across, thereby preserving the blood supply of that part of the bronchus which is to remain. The fibers of the pulmonary plexus of the vagus are then severed. At this point the vagus nerve is

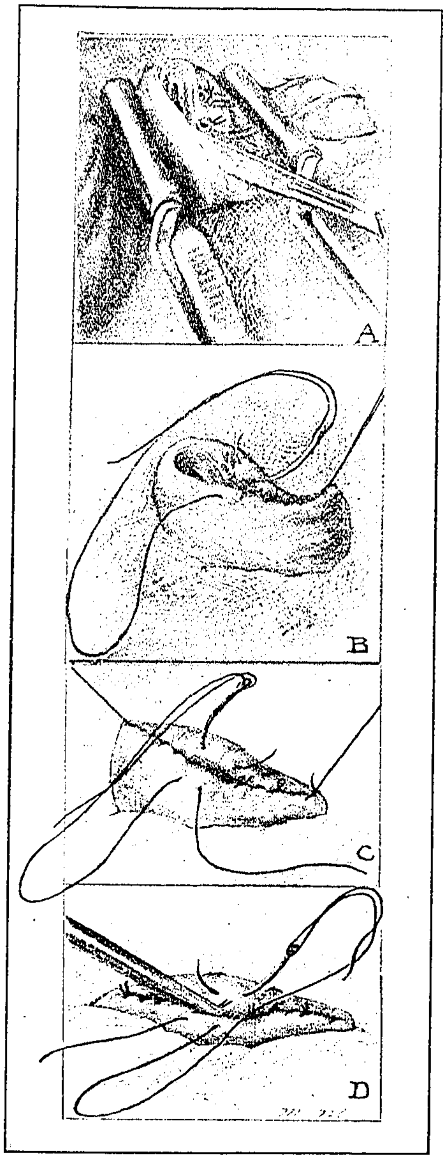

Fig. 4.—The various steps in the treatment of the main bronchus: *A*, the atraumatic division of the bronchus after protecting the pleural surfaces with gauze packs; *B*, the first inversion by means of a running Cushing suture (fine silk or catgut); *C* and *D*, further inversion accomplished by two rows of inverting interrupted mattress sutures (medium silk—Series B, catgut—Series A) applied only to the peribronchial tissues. In *C* the sutures are being introduced from right to left. In *D* the final suture of the last row is being placed. The inversion is more easily accomplished by placing the end sutures first. Gentle pressure applied by means of a hemostat to the ends of the underlying suture of the second row greatly facilitates further closure. Great care must be taken that the sutures do not penetrate the bronchial lumen of a contaminated bronchus.

gently displaced posteriorly to free it from the bronchus. This allows for a more adequate inversion of the bronchial stump without interfering with the vagus nerve. Great care, however, is taken not to strip the peribronchial tissues from the bronchus, which is now entirely freed. At this point two rubber shod bulldog clamps are put across the main bronchus above and below the proposed line of division. The bronchus is then divided with a scalpel, following the line indicated above. Both the scalpel and the resected lung are immediately discarded. If the bronchus is grossly contaminated with foul sputum (as was the case in the animals with experimentally produced chronic lung abscess), the mucosa of the stump is phenolized followed by alcohol and the first inversion is accomplished by a running Cushing suture of No. 0 chromic catgut. (See Fig. 4 B.) If the bronchus is not grossly contaminated, the phenolization is omitted and the first inversion carried out with a running Cushing suture of fine silk. Further inversion is then accomplished by two rows of inverting interrupted mattress sutures of medium silk. All sutures are introduced only through the peribronchial tissues, care being taken never to penetrate the bronchial lumen. The details of the technic are shown in the accompanying illustrations. The sutures are tied just tightly enough to approximate and not to strangulate the peribronchial tissues. By means of this technic the largest bronchial stump can be gradually and completely closed. After the closure is completed, the bronchial stump is tested for leaks by flooding the line of

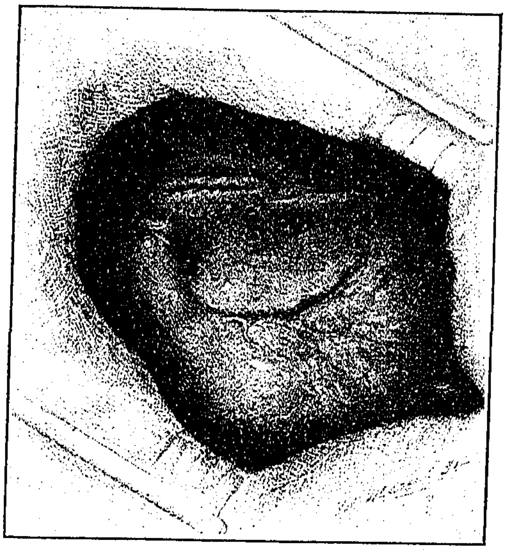

Fig. 5.—Note the retraction of the inverted bronchus into the mediastinum. The bronchus has just been tested for leakage by flooding the area with saline, prior to closure of the thoracic wound.

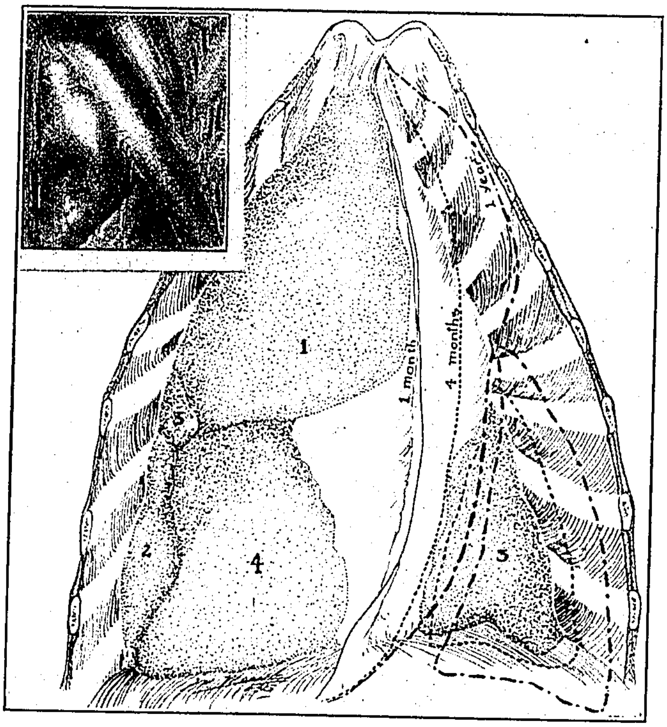

Fig. 6.—Note the gradual shifting of the mediastinal structures toward the operated side, slowly encroaching upon that pleural space, but never obliterating it as a potential cavity. Insert reveals the completely pleuralized stump as a rounded, slightly elevated area four weeks after operation. Note the absence of reaction and of adhesions.

closure with saline. If the entire procedure is carried out carefully, scarcely 2 c.c. of blood should be spilled into the pleural cavity. After a thorough inspection of the entire pleural cavity, the ribs are approximated by pericostal sutures of braided silk. The muscles are closed in layers with silk, and the skin is approximated with subcuticular sutures.

RESULTS

Prior to the introduction of the above technic 6 pneumonectomies were performed, with ligation en masse of the entire hilum. Of the 6, one animal survived and was sacrificed at the end of one year, 3 died of tension pneumothorax, one of hemorrhage, and one of secondary shock. (For details see Table I.) The mortality rate for the series was 83.4 per cent, while the incidence of bronchial fistulas in animals surviving more than forty-eight hours was 75%.

Greatly discouraged by the results with ligature en masse, the technic described above was carried out in 30 dogs (in some of which the lung was removed because of a chronic experimentally produced lung abscess). In the earlier part of this series employing the new method it was found that those bronchial stumps healed better and more animals survived in which black silk had been used as the suture material of the peribronchial tissues, regardless of whether the animal had a lung abscess. On the other hand, most of the animals in which chromic catgut had been used as a suture material to the peribronchial tissues developed a bronchial fistula and subsequently died of a tension pneumothorax. Because of these findings it was decided to run two series, in order to determine the possible relation of the suture material to the healing of the bronchial

TABLE I.

Ligation En Masse

Experiment	Length of Life	Cause of Death	Findings At Autopsy
		Series A. With Thirty-Day Chromic Catgut (No. 2)	
1. Dog 209	1 day	Acute gastric dilatation and hemorrhage from bronchial artery.	Massive left hemopneumothorax.
2. Dog 311	1 day	Circulatory collapse. Ligatures OK.	Right cardiac dilatation.
3. Dog 313	4 days	Bronchial fistula and tension pneumothorax.	Bronchial fistula. Hilar tissue distal to ligature necrotic.
4. Dog 194	6 days	Bronchial fistula and tension pneumothorax.	Bronchial fistula. Hilar tissue distal to ligature necrotic.
5. Dog 186	1 year	Sacrificed.	Entire left pleural cavity still patent. Stump retracted. Few adhesions.
		Series B. Black Silk	
1. Dog 186	4 days	Bronchial fistula and tension pneumothorax.	Bronchial fistula. Hilar tissue distal to ligature necrotic.

Mortality 83.4%

Incidence of bronchial fistula in animals surviving more than 48 hours 75.0%

TABLE II

Closure of Bronchus by Interrupted Inverting Sutures

Experiment	Length of Life	Cause of Death	Findings At Autopsy
	Series A.	With Twenty-Day No. 0 Chromic Catgut	
1. D. 183	2 days	Hemorrhage from pulmonary artery.	Massive left hemopneumothorax.
2. D. 218	3 days	Bronchial fistula and tension pneumothorax.	Bronchial fistula with marked shifting of mediastinum to right and marked compression of right lung. Small amount serous exudate.
3. D. 308	3 days	Ditto.	Ditto.
4. D. 365	4 days	Ditto.	Ditto.
5. D. 337	6 days	Ditto.	Ditto.
6. D. 367	6 days	Ditto.	Ditto.
7. D. 351	8 days	Ditto.	Ditto.
8. D. 301	10 days	Ditto.	Ditto.
9. D. 255	16 days	Empyema of left pleural cavity.	250 c.c. of fibrinopurulent exudate.
10. D. 385	3 wks.	Survived bronchial fistula which developed on fifth day. Sacrificed in three weeks.	Bronchial fistula still present, 50 c.c. purulent exudate. Moderate inflammatory reaction of pleural cavity.
11. D. 369	30 days	Sacrificed.	Pleural surfaces intact. No exudate. No adhesions.
12. D. 314	60 days	Sacrificed.	Pleural surfaces intact. No exudate. No adhesions.

Mortality 75.0%

Incidence of bronchial fistula 66.6%

TABLE III

Closure of Bronchus by Interrupted Inverting Sutures

Experiment	Length of Life	Cause of Death	Findings At Autopsy
		Series B. Black Silk	
1. D. 317	1 day	Acute cardiac dilatation.	Right-sided cardiac dilatation.
2. D. 200	1 day	Sacrificed.	Ligatures intact. No exudate.
*3. D. 374	4 days	Bronchial fistula and tension pneumothorax.	Sutures which had been applied only to the looser peribronchial tissues had cut thru.
4. D. 279	6 days	Empyema.	200 c.c. thick purulent exudate.
5. D. 337	1 week	Sacrificed.	Ligatures OK. No exudate. No adhesions. Pleural cavity intact.
6. D. 346	2 weeks	Sacrificed.	Ditto
7. D. 360	2 1/2 wk	Sacrificed.	Ditto
8. D. 353	3 weeks	Sacrificed.	Ditto
9. D. 334	3 1/2 wk	Sacrificed.	Ditto
10. D. 324	4 weeks	Sacrificed.	Ditto
11. D. 366	6 weeks	Sacrificed.	Ditto
12. D. 319	2 1/2 mo.	Sacrificed.	Ditto
13. D. 325	4 months	Sacrificed.	Ditto
14. D. 310	4 months	Sacrificed.	Ditto
15. D. 193	6 months	Sacrificed.	A few adhesions in costophrenic sinus.
16. D. 208	8 months	Sacrificed.	No adhesions. No exudate.
17. D. 361	10 mos.	Sacrificed.	No adhesions. No exudate.
18. D. 362	12 mos.	Sacrificed.	No adhesions. No exudate.

Mortality 16.6%

Incidence of bronchial fistula 5.5%

* Sutures intentionally applied to looser peribronchial tissues.

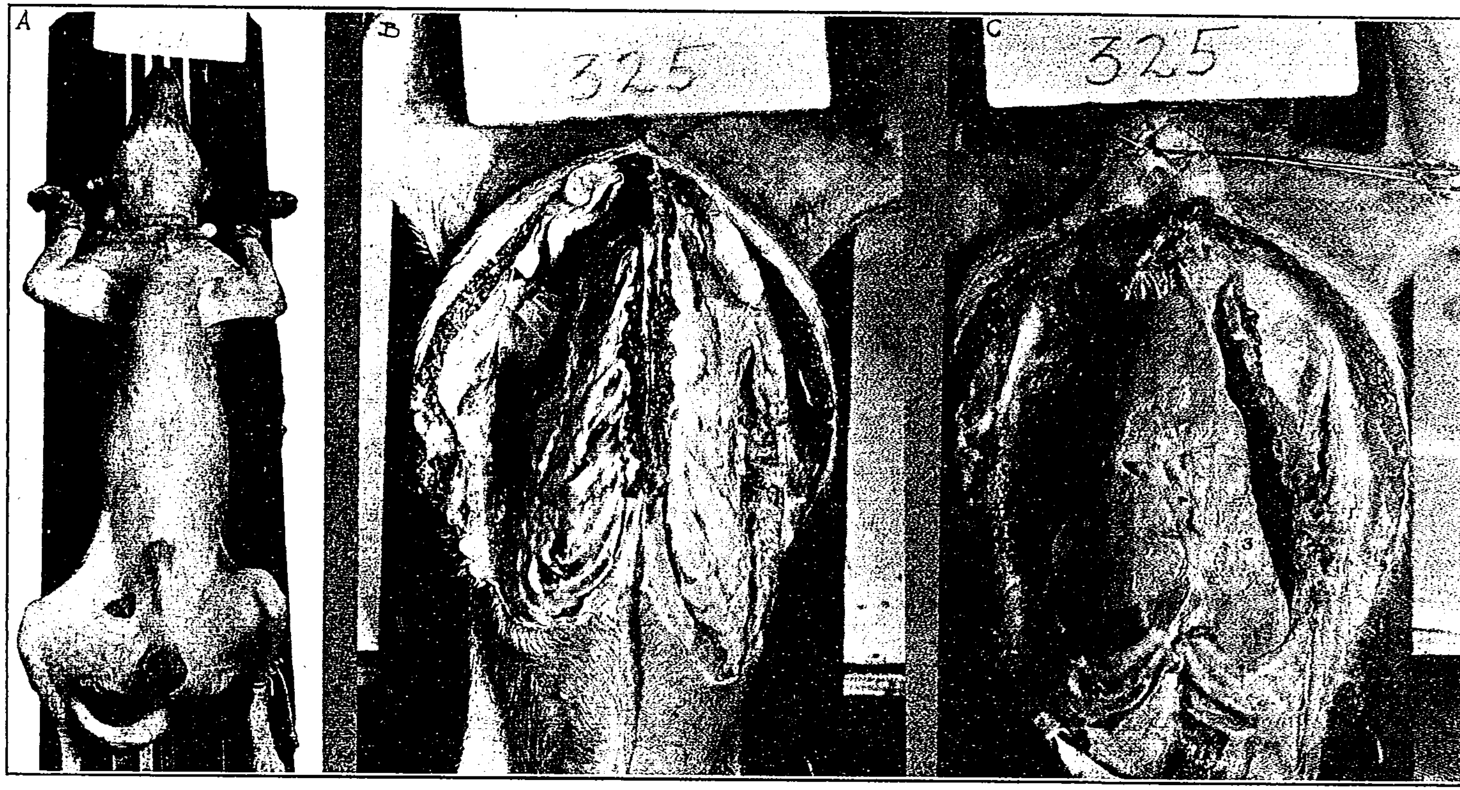

Fig. 7.—Anatomic changes four months after total pneumonectomy on the left. Note absence of gross deformity of thoracic wall in *A*. *B* shows some narrowing of intercostal spaces on the left. *C* shows the compensatory enlargement of the right lung with a shifting of the anterior mediastinum to the left, particularly in the upper chest, while the third lobe pushes the posterior mediastinum ahead of it as it advances to occupy the lower left chest.

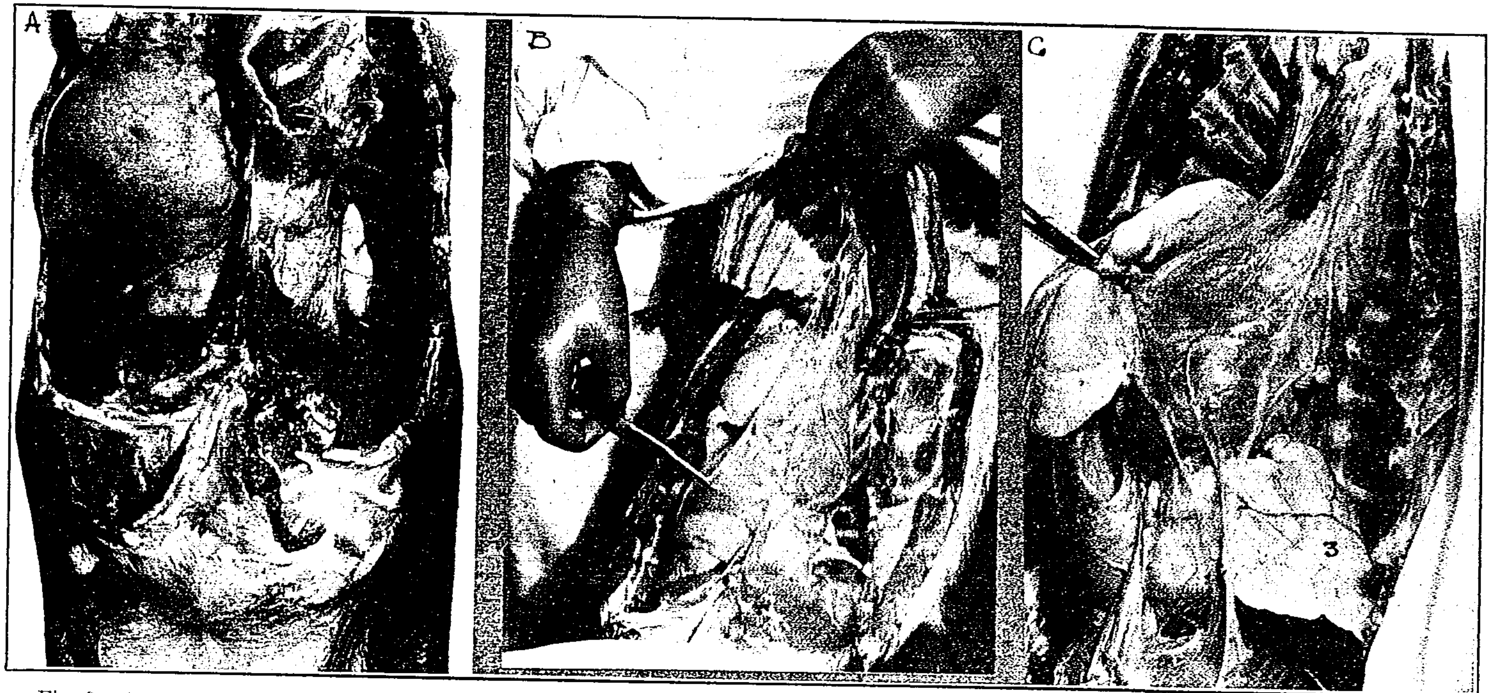

Fig. 8.—Anatomic findings in a dog one year postpneumonectomy. *A* shows absence of any elevation of the diaphragm on left side. *B* shows marked pocketing of both anterior and posterior mediastinum as the left pleural cavity is almost completely encroached upon by the remaining lung. *C* shows clearly the absence of adhesions, the shifting of the lower posterior portion of the mediastinum, and the dimpling of the mediastinum in the region of the bronchial stump.

stump. In Series A (12 dogs) in which twenty-day No. 0 chromic catgut was used as the suture material to the bronchial stump, the mortality rate was 75 per cent and the incidence of bronchial fistulas was 66.6 per cent. In Series B (18 dogs) in which fine and medium silk were used as the suture material of the bronchial stump, the mortality rate was 16.6 per cent and the incidence of bronchial fistulas was 5.5 per cent. Except for the difference in material, all details of technic were the same in both Series A and B. Only 3 animals developed empyema, 2 in the catgut series as against one in the silk series in spite of the fact that there was gross contamination of the bronchial stump in many of the animals operated upon.

The surviving animals were sacrificed at various intervals from one day to twelve months to study the healing of the bronchial stump. The following findings were noted. Twenty-four hours following pneumonectomy the stump was found to be intact but showed slight swelling and moderate injection on gross examination. Microscopically there was noted a dilatation of all peribronchial vessels along with some edema of the peribronchial tissues. There was also noted a polymorphonuclear invasion of the tissues close to the line of closure along with a deposit of fibrin on the surfaces. By the end of seventy-two to ninety-six hours the polymorphonuclear leucocytes had increased in number, and beginning fibroblastic proliferation was noted. The amount of inflammatory reaction observed was far more marked in those bronchial stumps closed with catgut (Series A) than in those in which silk alone (Series B) was used. This reaction was particularly marked in those stumps which had broken down and a bronchial fistula had formed, although the peri-

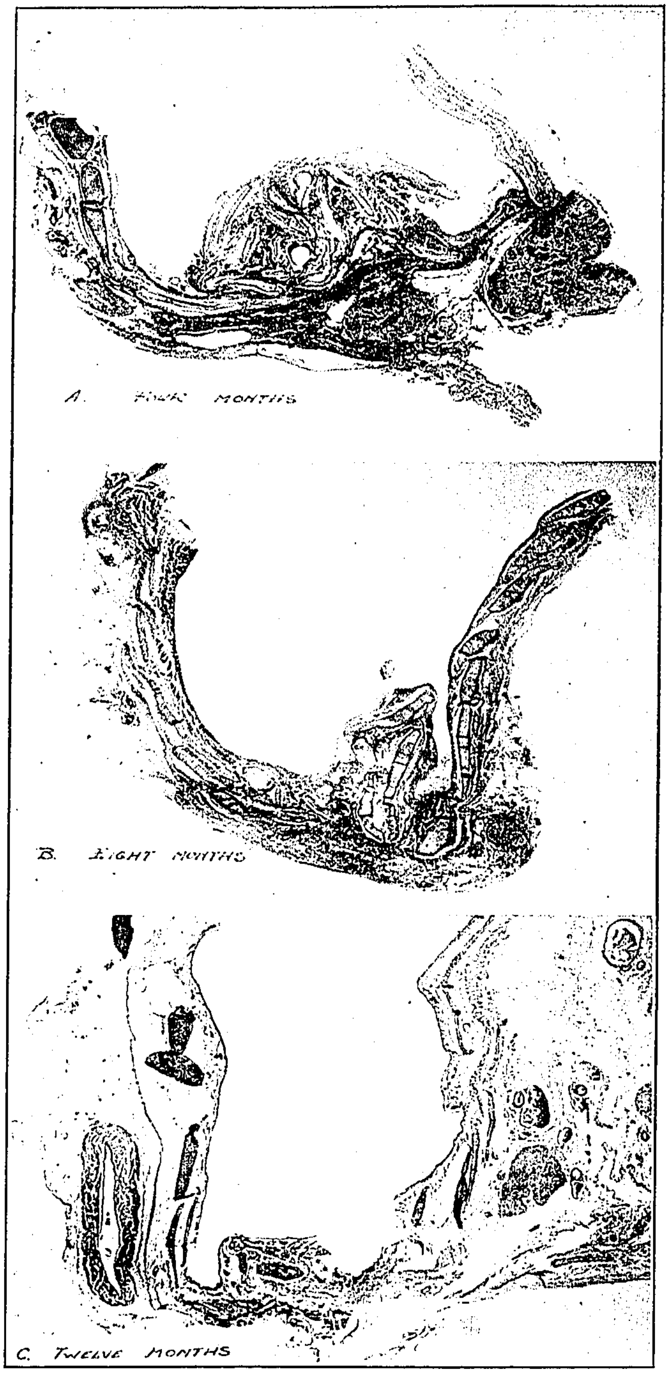

Fig. 9.—Histologic cross-sections of the bronchial stump four months, eight months, and twelve months postpneumonectomy. Disturbances of continuity are due to artefacts in the preparation of the sections.

bronchial tissues themselves were still viable. Grossly, the fistulas varied in size from 2 to 3 mm. in diameter to the size of a wide open bronchus. In many of them the catugt sutures were found lying loose along the fistulous tract. By the twelfth to fourteenth day the line of closure was noted to be sealed over with a loose network of newly formed granulation tissue. By the end of three to four weeks this had become more dense and the stump consequently more solid. By this time the external surface of the stump was pleuralized and the mucous membrane was starting to cover the inner surface of the bronchial stump. On subsequent studies (two, four, six, or eight months postpneumonectomy) the silk sutures were noted to be surrounded by a fibrous tissue capsule, which contained relatively few round cells and but few foreign-body giant cells. Vestiges of the silk were still present ten to twelve months after pneumonectomy. Not only the peribronchial tissues in the stump inverted by this method but the cartilages as well were found to remain viable in practically all instances. In only a few stumps was there noted a slow breaking down of the inverted cartilage.

The healing was in all cases brought about by the peribronchial tissues, although this was sluggish in contrast to the rate of healing seen in other tissues. It is felt that the advantage of silk as so evident in the experimental work lies in the fact that it is less irritating to tissues and that its tensile strength is not easily affected, and, consequently, it holds the peribronchial tissues in apposition during the relatively long period required for the solid repair of the bronchial stump.

In the animal which survived ligation en masse the cartilages beyond the point of ligation had completely degenerated and were replaced by fibrous tissue. The mucous membrane completely covered the inner surface of the stump by the sixth to eighth week.

As to the stump itself, it was found to retract into the mediastinal tissues so that the stump, which could be identified as a slightly rounded elevation three to four weeks postpneumonectomy, could by the fourth to sixth month be noted only as a dimpling of the mediastinal pleura and its outline along determined by palpation.

As to the fate of the pleural cavity--in none of the animals sacrificed following pneumonectomy in which closure of the bronchus was carried out with silk, was there any exudate found. Adhesions, also, were conspicuous by their absence. The pleural cavity on the pneumonectomized side remained a potential cavity, in spite of the fact that it was encroached upon by the gradual shifting of the mediastinal structures. By the end of one year, as demonstrated by roentgenograms and as seen at autopsy on animals following fixation of the organs in situ with formalin, the space was so encroached upon by the enlarging lung of the opposite side as to be occupied completely except for a small area at the apex and in the costophrenic sulcus. In spite of this the pleural space was still intact, and but few adhesions between the mediastinal and costal pleural surfaces were noted. These findings closely simulated those described by Heuer and Dunn.[22]

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II. Further studies indicating the importance of preserving the integrity of the peribronchial tissues in the care of the bronchial stump.

Review of the literature, not only of experimental lobectomy and pneumonectomy, but also of the clinical fields as well, reveals that the obtaining of a completely air-tight bronchial stump is the most difficult as well as the most important phase of the problem. The high incidence of bronchial fistulae along with the high incidence of pleural infection are to be ascribed essentially to the inherent difficulties in the care of the bronchial stump. The inherent difficulties are to be explained on the basis of the singular anatomic structure of the bronchus with its cartilaginous rings and meagre blood supply.

Not only the work of Bettman et al, but our earlier work (described above) indicates that the healing of the bronchial stump is brought about by the peribronchial tissues. The fact that the healing is brought about by these tissues, the blood supply to which is meager, indicates very clearly that the reparative process must needs be slow, and that a considerable time must elapse before the closure of the bronchial stump may be regarded as solid. Also, it suggests that any interference of the meager blood supply to these tissues by rough or careless handling will either impede healing or lead to necrosis with the inevitable development of a bronchial fistula.

Experimental Study With this in mind it was decided to run two series, in which the technique was to be the same (for details see our earlier work), except for the method of ligation of the bronchial arteries. In series A, the amount of trauma to the peribronchial tissues was to be reduced to a minimum by transfixing the small bronchial arteries with ligatures of fine silk. Thus, at the time of cutting across the bronchus there was no disruption or tearing of the peribronchial tissues. The closure of the bronchus was then performed in the routine manner (with a running Cushing mattress of fine silk followed by inversion with two layers of interrupted mattress sutures of fine silk). Ten dogs were operated upon in this series. In nine, the bronchus healed per primam without any complications. (See table A). In one animal, however, at the time of transfixation of the superior bronchial artery, the French needle pierced the vessel wall and a dissecting hematoma formed which was only controlled by the ligation of the vessel 8 m.m. proximal to the point of transection. Although the remaining bronchial arteries were transfixed at the level of transection, a bronchial fistula formed four days after pneumonectomy, which ended in the death of the animal from a tension pneumothorax within the next twenty-four hours. Autopsy revealed a bronchial fistula (4 m.m. in diameter) in the upper portion of the bronchus.

In series B, the same technique of resection of the lung was carried out, except for the treatment of the bronchial arteries. In these animals the bronchial arteries were freed up only sufficiently to pass two ligatures of fine silk under them by means of an aneurysm needle, one on the proximal and one on the distal side of the level of proposed transection of the bronchus.

TABLE A

Closure of Bronchus with Silk -- Transfixing the bronchial Arteries along line of transection of bronchus.

Experiment	Length of Life	Cause of Death	Findings at Autopsy
1. D 387	1 year	Living	Stump intact. No pneumothorax.
2. D 554	4 months	Distempter	Stump intact. Extensive broncho pneumonia of remaining lung.
3. D 548	5 months	Living	Stump intact. No pneumothorax.
4. D 549	5 months	"	" " "
5. D 564	5 months	"	" " "
6. D 568	5 months	"	" " "
7. D 543	5 months	"	" " "
8. D 583	2 months	"	" " "
9. D 563	2 1/2 mo	"	" " "
10. D 547	4 days	At time of pneumonectomy slight extravasation of blood into peribronchial tissues requiring ligation of one bronchial artery 6 m.m. proximal to transection.	Bronchial fistula with tension pneumothorax.

Mortality Rate 10%

Incidence of bronchial fistula 10%

TABLE B

Closure of Bronchus with Silk undermining the bronchial arteries only sufficiently to doubly ligate them without transfixtion.

Experiment	Length of Life	Cause of Death	Findings at Autopsy.
D. 451	3	Tension pneumothorax	Bronchial fistula with tension pneumothorax.
D. 453	4	" "	" " "
D. 461	4	" "	" " "
D. 465	3	" "	" " "
D. 533	5	" "	" " "
D. 544	4	" "	" " "
D. 519	4	" "	" " "
D. 547	3	" "	" " "

Mortality Rate 100%

Incidence of bronchial fistula 100%

The ligatures were tied down and the bronchial arteries then cut between ligatures. The lung was then removed and the bronchus closed in the routine manner. In all cases the closure was accomplished without any unusual incident. All eight animals in the series, however, died in from three to five days from a tension pneumothorax as the result of a break down of the bronchial stump. Autopsy revealed a bronchial fistula with marked shifting of the mediastinum in each case.

RESULTS

An analysis of the two series (see Tables A & B) reveals a ten percent incidence of bronchial fistulae in series A with a ten percent mortality as against the development of a bronchial fistula with a resulting tension pneumothorax in one hundred percent of the animals in series B. The only difference between the two series lay in the treatment of the bronchial arteries. In series A, the peribronchial tissues were not affected by the transfixation suture of the bronchial arteries; while in series B the peribronchial tissues were slightly disrupted by the procedure of freeing up of the bronchial arteries for a sufficient distance to allow the placement of the ligatures by means of an aneurysm needle. Although no bleeding was encountered after the latter procedure and inversion was accomplished without incident, all of the bronchi thus treated failed to heal "per primam" and developed bronchial fistulae.

It is felt that the above results further emphasize the important relation to bronchial healing of the preservation of the blood supply as well as the minimizing of the amount of trauma to the peribronchial tissues during the procedure of total pneumonectomy, (with transection at the level of the main bronchus).

AN EXPERIMENTAL STUDY OF SOME OF THE PHYSIOLOGIC CHANGES FOLLOWING TOTAL PNEUMONECTOMY

A. Historical Review

The development of the knowledge of respiration has come on comparatively late in the history of physiologic discovery. In 1666 Boyle[1] showed that air was necessary for life; by evacuating air from a chamber containing an experimental animal, by means of an air pump. Lower[2] and Mayow[3] (1673) found that the same "nitro-aerial spirit" necessary for the combustion of gun powder was also present in a limited proportion in the air. They believed that this "nitro-aerial spirit" was absorbed from the air in the lungs, and carried by the blood to the brain, separated off into the ventricles and passed down the supposed nerve tubules to the muscles. They explained the increased breathing, which accompanies muscular exercise, as a "necessary accompaniment of the increased consumption of the 'nitro-aerial spirit'" Lower and Mayow, thus, almost discovered oxygen. They also formed a sound physiologic concept of the relation between muscular work and increased breathing.

In 1667 Hooke[4] found that when the chest of an animal was opened so that the lung collapsed, the animal could be revived and kept alive by artificial respiration. The foundations of our present knowledge were thus laid down at Oxford, but not appreciated and research along this line was almost allowed to die out for the succeeding two-hundred years.

In the middle of the 18th century, Priestley[5] showed that "dephlogisticated air" disappears both in ordinary combustion and in animal respiration. He also showed that in the body, carbon and O_2 combined to form CO_2 and that this is the source of animal heat. He also found that during muscular work, the consumption of O_2 and the output of CO_2 are increased. Mayer[6] (1845) pointed out that the ultimate source of muscular movement is oxidation. Every exact experiment made since then on this subject has confirmed Mayer's conclusion -- that the consumption of O_2 is a main feature in the persistent coordinated activity which we call life. Magnus[7] (1845) showed definitely that less O_2 and more CO_2 are given off from venous than arterial blood on exposing it to a vacuum. The mercurial blood gas pump was gradually perfected (Meyer, Ludwig[8] and Pflüger[9,10,11, 12]) and hemoglobin was demonstrated to be the carrier of O_2.As can be seen, definite progress in this field paralleled the development of chemistry, but more particularly of the mercurial blood gas pump.

From the time of Biondi's[13] early experiments (1882), it has been known that animals could survive the removal of the lung on one side. It was, however, not until the work of Heuer and Andrus[14] in 1922 that any attempt was made to study the compensatory adjustments of the organism to pneumonectomy. With their animals under resting conditions they noted:

1. An increase in alveolar carbon dioxide lasting for thirty days.
2. A fall in alveolar oxygen returning to its pre-operative level in twenty-eight to sixty-six days.

3. A slight increase in the blood carbon dioxide falling to normal by the 25th day.
4. A marked fall in the blood oxygen content up to the eleventh day, returning to normal by the twenty-fifth to thirtieth day.

The following year Andrus[15] reported a 42% decrease of the total lung volume immediately following pneumonectomy with a return to the pre-operative level in twenty to twenty-six days. He also noted a transient increase in the pulse rate and the blood flow through remaining lung, which persisted for ten days and later fell to slightly below the pre-operative level.

Wiggers[16] (1921), Underhill[17] (1921), Haggart and Walker[18] (1923) measured the increase in the pressure in the pulmonary artery produced by the occlusion of its main branches. Scarff[19] (1926) reported an immediate increase (30 to 50%) in the systolic pulmonary arterial pressure following pneumonectomy, returning to the pre-operative level in from seven to twenty-one days. Churchill[20] (1929) demonstrated that the burden thrown on the lung by a sudden increase in blood flow is not entirely borne by the increase in pulmonary ventilation, but is in part compensated for by an increase in the area of functional diffusing surface. This may be brought about by the opening up of reserve capillaries, according to the concept of Wearn[21]. Drastich[22] (1934) reported that reduction in active pulmonary tissue by 50% does not embarrass the organism when engaged in moderate exercise (running on the level for thirty minutes), but that more strenuous exercise such as swimming results in more fixed acid formation than normal.

B. EXPERIMENTAL STUDY

In the lung as in any other organ, there exists a large functional reserve which may be called into play by increasing demands upon the respiration. This intrinsic lung function possesses a power of prompt adaptation to the changing demands made upon it. Since this function is so intimately associated with the heart, it is a question whether it would not be more accurate to speak of these changes as changes in cardio-respiratory reserve.

In the course of a previous experimental study of the factors responsible for the healing of the bronchial stump following pneumonectomy, it was noted that several of the animals in the paddock who were the most pugnacious and belligerent were pneumonectomized animals. In consequence, thereof, the following study was undertaken to evaluate in accurate physiologic terms, the degree of cardio-respiratory impairment at various intervals following pneumonectomy. The study was to be carried on to that point where the animals showed no further compensatory change. In short, the attempt was made to assay the degree to which the animals could in time achieve a functional adaptation to the anatomic removal of approximately 50% of their pulmonary tissue.

Since it is only under conditions of actually increased tissue demands that the efficiency of the cardio-respiratory system can be tested, it was decided to study the physiologic response of a series of trained young healthy dogs to varied amounts of moderate strain. Studies were made of alteration in pulse, respirations, temperature; blood gas changes both in arterial and venous bloods;

oxygen debt etc. during treadmill runs of one, one and a half and two hours. In addition the animals were submitted to absolute strain by means of the anoxemia test (to be described later) and the critical level of oxygen determined. In addition tracings were made of the respiratory dynamcs at the resting level, the subtidal lung capacity was determined by the method of Chrisite, and the blood hemoglobin measured in terms of grams hemoglobin per 100 c.c. In short, these animals were to be their own controls - any change following pneumonectomy could be compared with pre-operative values, thereby eliminating the possible error of individual variations of the controls.

The animals were then pneumonectomized, the left lung being removed by the method described by [redacted] the author.[23] An interval of two months was allowed in order to assure the recovery of the animals to the point that they could bear up under the rigors of the tests. The above observations were then repeated at monthly intervals.

I. Experiments Dealing With Varying Degrees of Moderate Strain.

In all of the exercise experiments, the same routine was followed. The pulse, respiration and temperature were determined with the animal at rest. The bloods were then drawn and introduced under oil into vials containing potassium oxalate crystals. The arterial blood was obtained by femoral artery puncture and the venous blood drawn from the saphenous vein. The animal (previously trained) was then placed on the motor driven treadmill and run for a given period (traversing at a fast walk 2300 meters in the one hour run, 3450 meters in the one and a half hour run and 4600 meters in the two hour run). At the end of the run, the bloods were drawn, pulse, respiration and temperature changes noted. Both arterial and venous bloods were obtained within one to two minutes following the completion of the run. The oxygen and carbon dioxide determinations were made on both the arterial and venous bloods in a Van Slyke and Neill manometric blood gas apparatus. The oxygen capacity of the arterial bloods both before and after the runs were then determined and the percentage of change in the saturation of the arterial blood during the run noted. It is felt as a result of this study that the study of the changes in the arterial bloods under condition of strain brings out the integration of the three main factors in the respiratory system, namely the effectiveness of ventilation, diffusion of gases and perfusion of the lungs. The following are the results obtained.

(A) One Hour in the Treadmill (2300 meters)

The normal pre-pneumonectomized animals after one hour on the treadmill showed a slight rise in temperature, pulse and respiration, but did not show any decrease in the saturation of the arterial blood. Two months following pneumonectomy the rise in temperature was practically doubled, while the pulse acceleration was tripled. The respirations were increased but slightly and there was no decrease in the saturation of the arterial blood. On the succeeding runs, there was a tendency for the pulse and temperature rise to return toward the pre-operative levels, the animals showing, however, a slightly greater increase in respiratory rate and a tendency toward slight decrease in the saturation of the arterial blood. For details see Chart #1 and Table #1. and #2.

(B) One and one half Hours in the Treadmill (3450 meters)

The normal (pre-pneumonectomy) animals showed a moderate

Fig. 1.

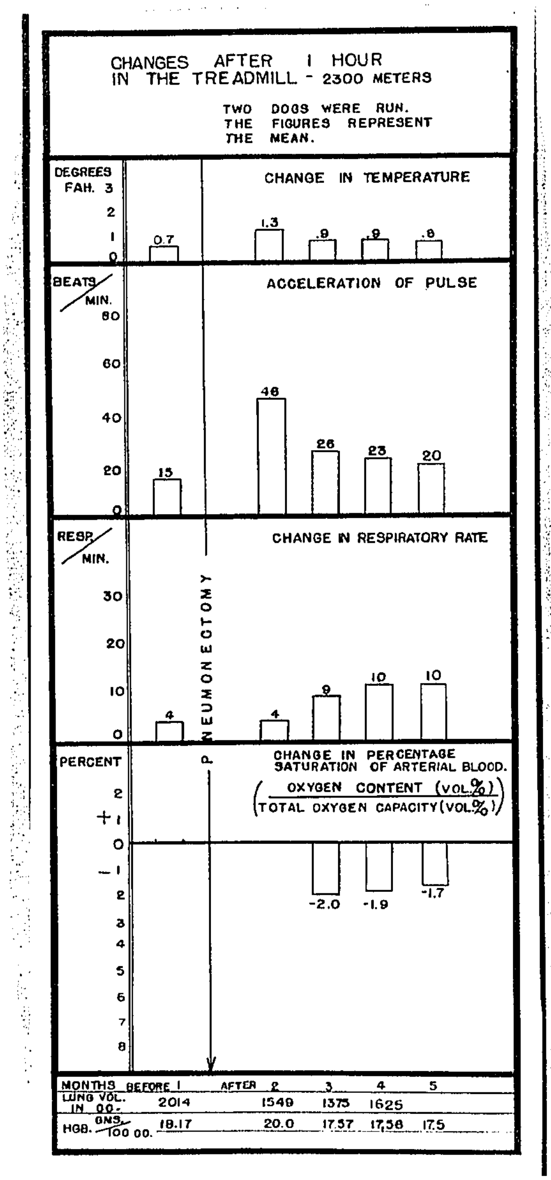

CHANGES AFTER 1 HOUR
IN THE TREADMILL - 2300 METERS
TWO DOGS WERE RUN.
THE FIGURES REPRESENT
THE MEAN.
DEGREES FAH.
CHANGE IN TEMPERATURE
0.7
1.3
.9
.9
.8
BEATS/MIN.
ACCELERATION OF PULSE
15
48
26
23
20
RESP./MIN.
CHANGE IN RESPIRATORY RATE
4
4
9
10
10
PNEUMONECTOMY
PERCENT
CHANGE IN PERCENTAGE
SATURATION OF ARTERIAL BLOOD.
OXYGEN CONTENT (VOL.%)
TOTAL OXYGEN CAPACITY (VOL.%)
-2.0
-1.9
-1.7
MONTHS BEFORE 1 AFTER 2 3 4 5
LUNG VOL. IN CC. 2014 1549 1375 1625
HGB. GMS./100 CC. 18.17 20.0 17.57 17.58 17.5

Fig. 2.

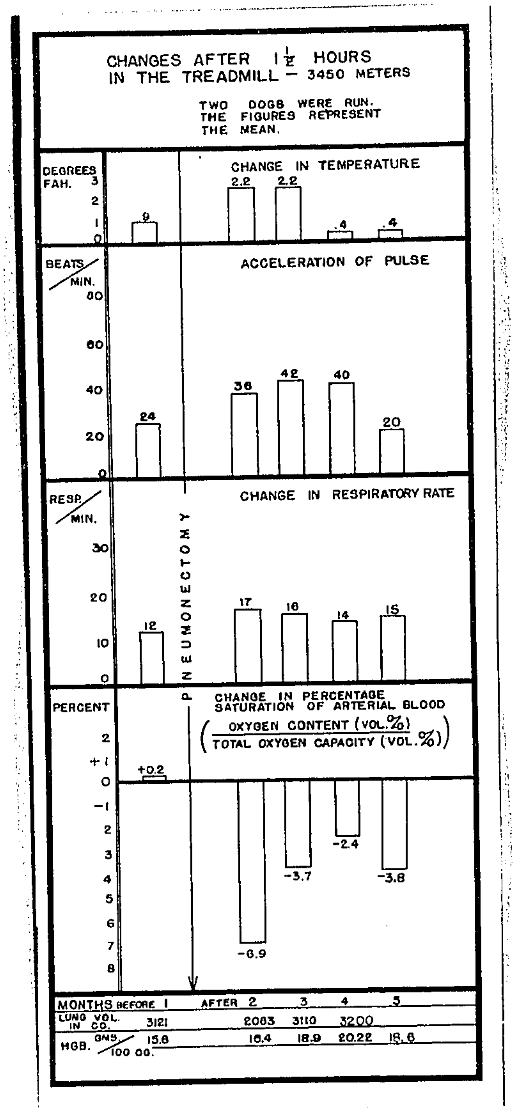
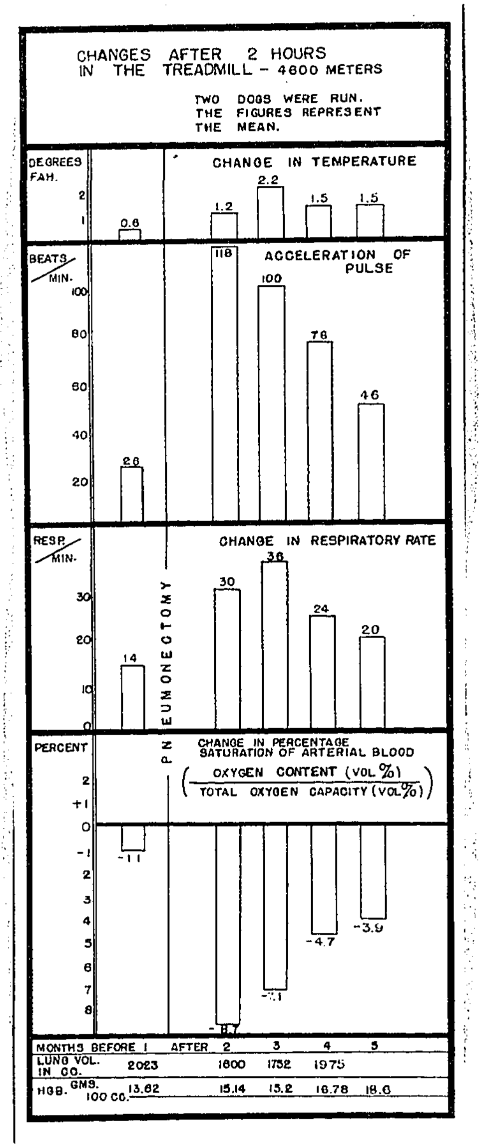

CHANGES AFTER 1½ HOURS IN THE TREADMILL — 3450 METERS
TWO DOGS WERE RUN. THE FIGURES REPRESENT THE MEAN.
DEGREES FAH.
CHANGE IN TEMPERATURE
.9
2.2
2.2
.4
.4
BEATS/MIN.
ACCELERATION OF PULSE
24
36
42
40
20
RESP./MIN.
CHANGE IN RESPIRATORY RATE
12
17
16
14
15
PNEUMONECTOMY
PERCENT
CHANGE IN PERCENTAGE SATURATION OF ARTERIAL BLOOD
(OXYGEN CONTENT (VOL.%) / TOTAL OXYGEN CAPACITY (VOL.%) %)
+0.2
-6.9
-3.7
-2.4
-3.8
MONTHS BEFORE 1 AFTER 2 3 4 5
LUNG VOL. IN CC. 3121 2063 3110 3200
HGB. GMS/100 CC. 15.8 16.4 18.9 20.22 18.6

Fig. 3.


CHANGES AFTER 2 HOURS IN THE TREADMILL - 4600 METERS
TWO DOGS WERE RUN. THE FIGURES REPRESENT THE MEAN.
DEGREES FAH.
CHANGE IN TEMPERATURE
0.6
1.2
2.2
1.5
1.5
BEATS/MIN.
ACCELERATION OF PULSE
26
118
100
76
46
RESP./MIN.
CHANGE IN RESPIRATORY RATE
14
30
36
24
20
PNEUMONECTOMY
PERCENT
CHANGE IN PERCENTAGE SATURATION OF ARTERIAL BLOOD
(OXYGEN CONTENT (VOL %) / TOTAL OXYGEN CAPACITY (VOL %))
-1.1
-4.7
-3.9
MONTHS BEFORE 1 AFTER 2 3 4 5
LUNG VOL. IN CC. 2023 1800 1732 1975
HGB. GMS./100 CC. 13.62 15.14 15.2 16.78 18.6

increase in temperature, pulse, and respirations following the run of 3450 meters, but they did not show any decrease in the saturation of the arterial blood. Two months following pneumonectomy they showed a more marked elevation of temperature, pulse and respirations, and there was a marked decrease in the saturation of the arterial blood. On succeeding runs the pulse tended to remain elevated although the respiratory rate was diminished and the degree of unsaturation was markedly decreased. Clinically these animals showed much more embarrassment post-pneumonectomy than did the one hour group. Review of the data on Chart #2 and Table #3, and #4. reveals the cause.

(C) Two Hours in the Treadmill (4600 meters)

The normal pre-pneumonectomy animal showed a moderate increase in temperature, pulse, and respirations along with a slight decrease in the saturation of the arterial blood. Following pneumonectomy the animal showed a very alarming elevation of the pulse associated with a very marked decrease in the saturation of the arterial blood, the arterial blood being almost venous in character. The animals' condition when taken off the treadmill was very alarming, almost completely exhausted. Three months following pneumonectomy its condition was less alarming. Four months post pneumonectomy, the animal although showing a considerable elevation of pulse, respiration and temperature, did not show any considerable distress. Simultaneously, there was a decrease in the degree of unsaturation of the arterial blood. For details see chart #3 and table #6.

II <u>Absolute Strain:- As Measured by the Anoxemia Test.</u>

In 1878, Paul Bert[24] in studying the effects of lowered oxygen pressure, noted that sparrows died when the oxygen dropped to 3.5%. Haldane[25] has shown that in humans when a small quantity

Dog #543

Table 1.

One Hour in Treadmill

	Temp.		Pulse		Respiration		Arterial Blood					Venous Blood		Hemo-globin	Lung Volume	Anoxemia Test
	Be-fore	After exer.	Be-fore	After exer	be-fore	After exer.	Be-fore	After exer	O_2Capacity Befor	Aft.	Change O_2 Sat	Be-fore	After exer			
Before Pneu	101.8	102.4	122	140	42	30	$O_2$24.9 / $CO_2$33.1	22.2 / 40.8	26.5	23.6	0.0%	$O_2$17.7 / $CO_2$34.4	20.5 / 34.4	18.58	1050	5.01%
Pneumonectomy																
2 mos. after	101.6	103	90	148	30	34	$O_2$27.4 / $CO_2$32	30.6 / 35	28.5	31.0	2.6%	O_2 / CO_2	22.2 / 35.6	21.3	970	15.9%
3 mos. after	102	102.8	106	128	20	28	$O_2$22.3 / $CO_2$37.4	20.4 / 36.5	25.3	23.3	.6%	$O_2$17.6 / $CO_2$37.4	20.2 / 36.4	18.5	1049	14%
4 mos. after	102	102.6	88	120	26	36	$O_2$23.9 / $CO_2$35.7	23.3 / 37.9	24.8	24.7	2.1%	$O_2$14.6 / $CO_2$40.7	13.7 / 41.8	17.0	1060	9.4%
5 mos. after																7.6%

Dog #548.

Table #2.

One Hour in Treadmill

	Temp.		Pulse		Respiration		Arterial Blood					Venous Blood		Hemo-globin	Lung Volume	Anoxemia Test
	Be-fore	After exer	Be-fore	After exer	Be-fore	After exer	Be-fore	After exer	O_2 Capacity Be	Aft.	Change O_2 Sat.	Be-fore	After exer.			
Before Pneu.	101	101.8	88	100	16	20	O_2 24.2 / CO_2 33.0	22.0 / 40.0	25.8	23.6	0.7%	O_2 17.5 / CO_2 34.2	19.5	17.76	3023	5.4%
Pneumonectomy																
2 mos. after	101.4	102.6	88	120	16	20	O_2 25.3 / CO_2 40.7	24.3 / 40.5	25.6			O_2 16.7 / CO_2 44.0	22.7 / 39.2	18.73	2128	10.8%
3 mos. after	102.2	103.2	90	120	20	30	O_2 21.4 / CO_2 44.5	20.9 / 41.9	22.8	23.1	3.4%	O_2 18.5 / CO_2 45.9	17.1 / 41.7	16.64	1700	13.6%
4 mos. after	102.2	103.4	96	110	20	34	O_2 33.2 / CO_2 42.2	22.5 / 39.4	24.6	24.3	1.7%	O_2 20.7 / CO_2 44.1		18.13	2211	9.2%
5 mos. after	102	102.8	100	120	20	30	O_2 23.2 / CO_2 42.2	22.5 / 39.4	24.6	24.3		O_2 20.7 / CO_2 44.1	24.9 / 38.8	18.1		8.3%

Dog #554

Table #3.

One and one half Hours in Treadmill

	Temp.		Pulse		Respiration		Arterial Blood					Venous Blood		Hemo-globin	Lung Volume	Anoxemia Test
	Be-fore	After exer.	Be-fore	After exer	Be-fore	After exer	Be-fore	After exer.	O_2 Capacity Before	After	Change in O_2 Sat.	Be-fore	After exer			
Before Pneu.	102.2	102.8	72	96	16	24	O_2 19.2 CO_2 33.5	17.3 33.4	21.5	19.4	0%	O_2 16.9 CO_2 41.5	15.8 34.	13.83	3650	5.6%
Pneumonectomy																
2 mos. after Pneu.	103.6	104.2	100	140	20	40	O_2 22.0 CO_2 40.8	17.8 40.0	23.2	20.4	6.8%	O_2 17.7 CO_2 50.9	18.5 37.6	16.04	2450	14.4%
3 mos. after. Pneu.	103.4	104.6	98	140	24	42	O_2 18.6 CO_2 50.9	18.9 37.6	20.3	21.3	3.7%	O_2 15.8 CO_2 44.4	14.0 52.3	14.77	3384	12.6%
4 mos. after		Dog died of distemper.														

Dog #568.

Table #4.

One and One Half Hours in Treadmill

	Temp.		Pulse		Respiration		Arterial Blood					Venous Blood		Hemo-globin	Lung Volume	Anoxemia Test
	Be-fore	After exer	Be-fore	After exer	Be-fore	After exer	Be-fore	After exer	O_2 Capacity Be	Aft	Change O_2 Sat.	Be-fore	After exer.			
Before Pneu	101	102	100	124	20	36	O_2 19.15 CO_2 33.	17.3 32.56	21.52	19.4	0.2%	O_2 11.96 CO_2 43.5	13.96 35.8	15.6	3121	5.02%
Pneumonectomy																
2 mos. After	99.4	102.8	112	150	36	50	O_2 21.7 CO_2 44.3	20.6 32.2	22.5	23.0	6.9%	O_2 15 CO_2 46.7	16.4 38.2	16.4	2163	10.2%
3 mos. After	99.8	102.8	110	152	30	44	O_2 55 CO_2 33.4	21.6 32.7	26.1	22.6	4.0%	O_2 18.1 CO_2 36.1	18.3 34.2	18.9	3109	14.3%
4 mos. After	101.4	101.8	120	160	36	50	O_2 25.4 CO_2 31.4	25.4 33.8	27.4	28.1	2.4%	O_2 17.1 CO_2 36.7	23.3 45.2	20.22	3217	9.0%
5 mos. After	100.8	101.2	100	120	32	54	O_2 24.4 CO_2	22.8	25.4	24.7	3.8%	$\frac{O_2}{CO_2}$		18.6		7.7%

Dog #549.

Table #5.

One and Three-fourth Hours in Treadmill

	Temp.		Pulse		Respiration		Arterial Blood					Venous Blood		Hemo-globin	Lung Volume	Anoxemia Test
	Before	After exer.	Before	After exer	Before	After exer	Before	After exer.	O_2 Capacity Before	O_2 Capacity After	Change in O_2 Sat.	Before	After exer			
Before Pneu.	103.2	100.6	100	100	22	30	O_2 18.2 / CO_2 37.6	17.6 / 36.5	18.82	18.55	1.7%	O_2 17.65 / CO_2 32.9	15.0 / 36.9	13.67	3600	5.62%
Pneumonectomy																
2 mos. After	102.2	102.8	110	130	20	20	O_2 17.3 / CO_2 37.1	18.2 / 31.4	17.3	19.3	5.7%	O_2 13.7 / CO_2 39.4	16.7 / 47.5	14.03	2135	13.3%
3 mos. After	103	103.6	110	130	24	40	O_2 21.7 / CO_2 35.6	20.3 / 40.1	23.3			O_2 17.8 / CO_2 39.6	20.3 / 38.7	17.01	2046	10.3%
4 mos. After	103	104.2	104	104	24	30	O_2 22.3 / CO_2 36.8	30.2 / 35.1	23.3	22	3.9%	O_2 22.3 / CO_2 36.8	20.2 / 35.1	17.01	3900	7.2%
5 mos. After	102.6	103	110	120	24	30	O_2 22.2 / CO_2	21.8	24.0					18.6		7.5%

Dog #564

Table #6.

Two Hours in Treadmill

	Temp.		Pulse		Respiration		Arterial Blood					Venous Blood		Hemo-globin	Lung Volume	Anoxemia Test
	Be-fore	After exer.	Be-fore	After exer	Be-fore	After exer	Be-fore	After exer.	O_2 Capacity Before	After	Change O_2 Sat.	Be-fore	After exer			
Before Pneumo-nectomy	101	101.6	94	120	20	34	O_2 18.2 / CO_2 37.6	17.6 / 36.5	18.82	18.55	1.1%	O_2 17.54 / CO_2 32.9	15.0 / 36.4	13.62	2025	7.0%
Pneumonectomy																
2 mos. after pneu.	101.4	102.6	92	210	20	50	O_2 20.3 / CO_2 35.7	17.9 / 32.8	20.3	19.6	8.7%	O_2 18.5 / CO_2	17.2 / 33.1	15.14	1600	12.5%
3 mos. after pneu.	102.4	103.6	100	200	24	60	O_2 19.4 / CO_2 33.1	18.6 / 34.2	21.0	21.8	7.1%	O_2 15.5 / CO_2 32.0	19.4 / 33.0	15.2	1752	12.5%
4 mos. after pneu.	102.8	104.2	120	196	20	44	O_2 22.3 / CO_2 33.7	20.5 / 29.7	23	22.2	4.7%	O_2 20.1 / CO_2 33.1	16.7 / 34.7	16.78	2484	9.5%

(6000 c.c.) of air is rebreathed continuously up to the verge of loss of consciousness the carbon dioxide being absorbed, the inspired air contained 4.8% oxygen and the alveolar air 3.7% oxygen. With the onset of acute anoxemia there is noted first an increase in the respiratory and circulatory rate along with a great temporary rise in blood pressure. With further increase of the degree of anoxemia the heart beats like the respirations become more and more feeble. According to Haldane, with acute anoxemia the respiratory center becomes very susceptible to fatigue and the respirations seem almost always to fail before the heart fails.

On the basis of these facts it was felt possible to devise a test which would put the ultimate degree of strain on the cardio-respiratory unit and still be able to spare the animal. The animals were made to breathe room air in a closed system (see Diagram #1), the carbon dioxide being removed and the oxygen gradually being evacuated to a certain critical point. This end point was found to be quite definite and to be recognized by the following phenomena; loss of consciousness with wide dilatation of the pupils, loss of both urinary and rectal sphincter control, cessation of respirations (except for occasional gasps) along with complete loss of all motor tone. The loss of tonus of the rectus muscle along with relaxation of the muscles in the extremities was found to be the most clear cut end-point. At this point although respiratory movements had practically cease, the heart is still beating. All of the animals were carried to this end-point and were then cut out of the closed system by means of a three-way valve and resuscitated with oxygen. Only occasionally was it found necessary to resort to artificial respiration. Samples taken from the system at the end

Diagram.

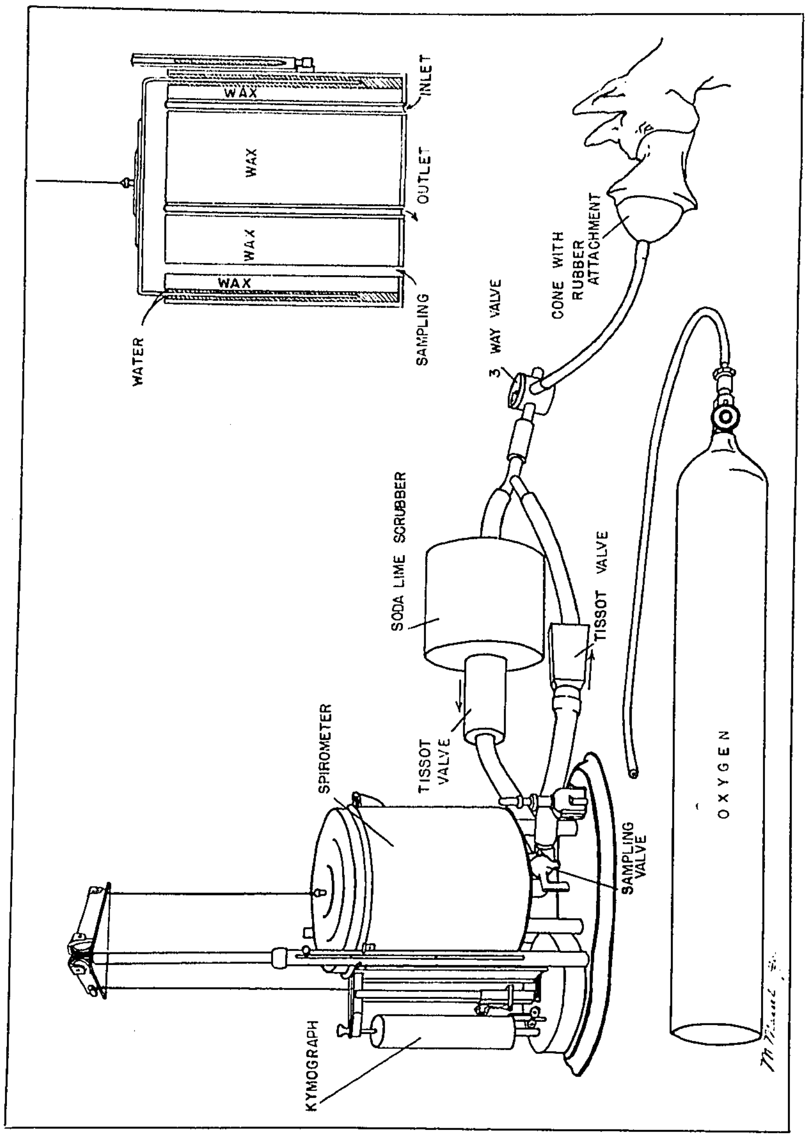
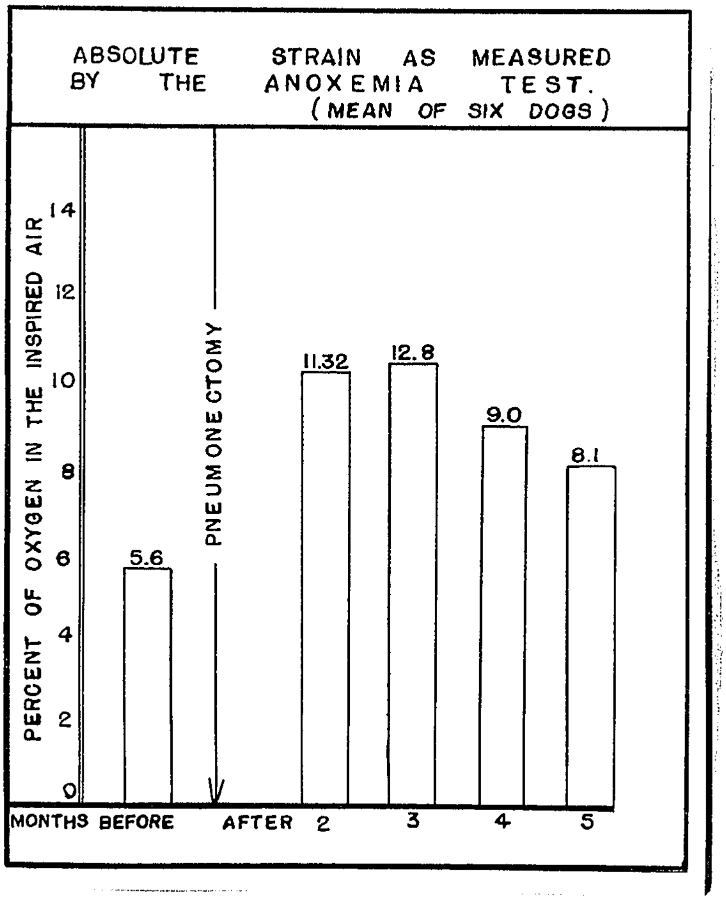

WAX
WAX
WAX
WAX
INLET
OUTLET
SAMPLING
WATER
3 WAY VALVE
CONE WITH RUBBER ATTACHMENT
SODA LIME SCRUBBER
TISSOT VALVE
TISSOT VALVE
SPIROMETER
SAMPLING VALVE
KYMOGRAPH
OXYGEN

Fig. 4.


ABSOLUTE STRAIN AS MEASURED BY THE ANOXEMIA TEST.
(MEAN OF SIX DOGS)
PERCENT OF OXYGEN IN THE INSPIRED AIR
0
2
4
6
8
10
12
14
PNEUMONECTOMY
5.6
11.32
12.8
9.0
8.1
MONTHS BEFORE
AFTER 2
3
4
5

of the run were collected over mercury either in Bailey bottles or Hempel pipettes and analyzed in the manometric Van Slyke. The samples taken before pneumonectomy showed a clear cut end-point between 5 and 5.6% oxygen.

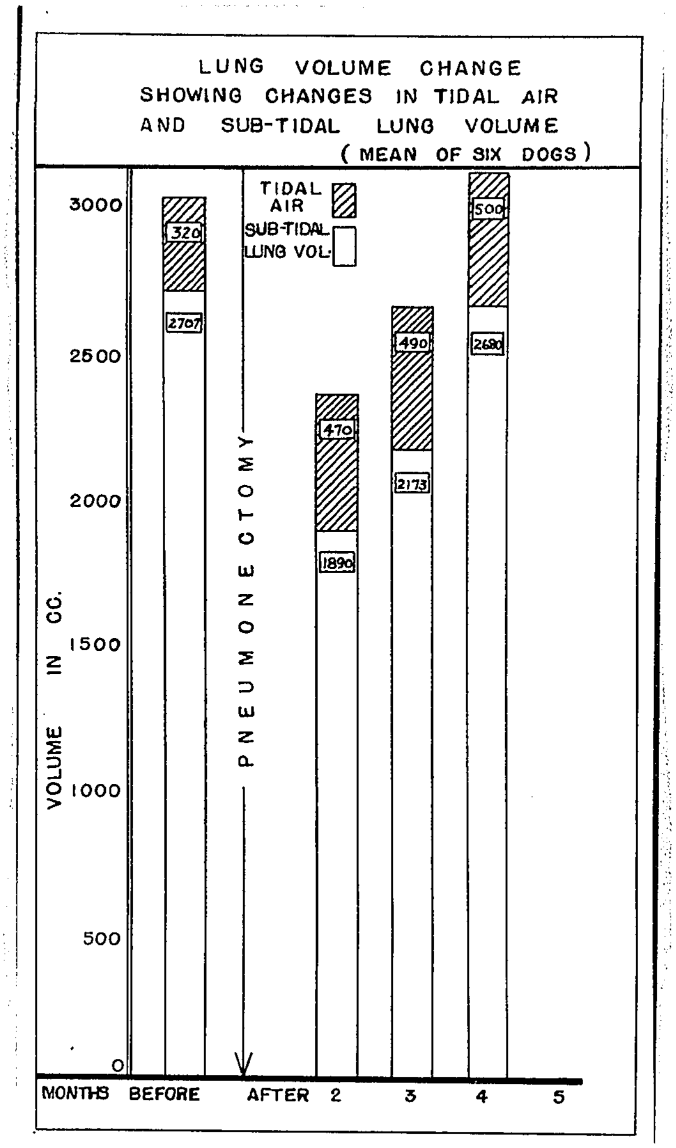
Following pneumonectomy at the end of the two month interval, this has risen to practically twice its previous level (11.3%). At the third month the level of oxygen tension was slightly increased to 12.88 (possibly due to an epidemic of acute respiratory infection which swept through the dog house). By the fifth month the level had decreased to about 8.1%. (For details see Chart #4).

III <u>Statics and Dynamics of the Respiratory System</u>

The compensatory enlargement of the lung remaining after one sided pneumonectomy has long been an established fact. There is still, however, little knowledge as to the exact nature of this enlargment. The question of compensatory emphysema vs. a true compensatory hypertrophy is still an unsettled one. Laennec[26] (1819) was the first to speak of pulmonary hypertrophy. In 1929, Celice[27] again raised the question of "L'hypertrophie du poumon". Hilber[28] (1934) claimed that in rats following the removal of one lobe, the remaining lung areas compensate for the loss not only by a compensatory emphysema but by a genuine regeneration with the new formation of perfectly efficient lung tissue with corresponding new bronchi, new vessels and new respiratory alveoli.

In order to correlate the change in lung volume with the changes in cardio-respiratory reserve, subtidal lung volume determinations were made at intervals corresponding to the functional

Fig. 5.


LUNG VOLUME CHANGE
SHOWING CHANGES IN TIDAL AIR
AND SUB-TIDAL LUNG VOLUME
(MEAN OF SIX DOGS)
TIDAL AIR
SUB-TIDAL LUNG VOL.
VOLUME IN CC.
3000
2500
2000
1500
1000
500
0
320
2707
470
1890
490
2173
500
2690
PNEUMONECTOMY
MONTHS BEFORE AFTER 2 3 4 5

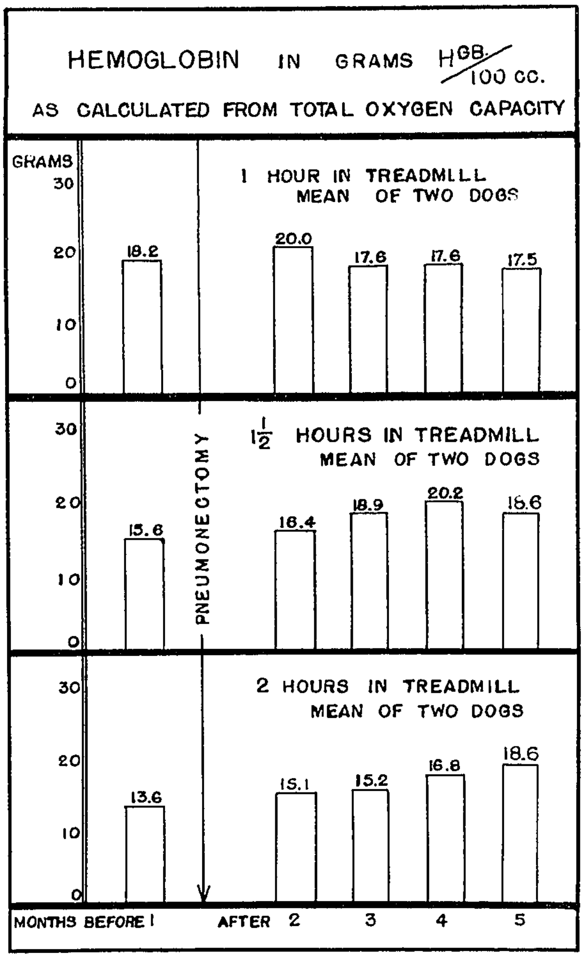
tests. The determinations were made according to the method described by Christie.[29] The remaining lung was noted to enlarge so that by the two months following pneumonectomy, the subtidal lung volume had reached 60 to 80% of the pre-operative level. Succeeding observations revealed a ~~gradual~~ return toward the normal level. (see chart #5)

The dynamics of the respiratory apparatus at the resting level can best be studied by means of spirometry. Considerable information can thus be obtained. Permanent tracings were kept of the animals' respirations under resting conditions, both before and at intervals after pneumonectomy. An analysis of the records revealed an increase in both the rate and depth of breathing under resting conditions following pneumonectomy, with a very considerable increase (35 to 50%) in the tidal air. (See chart #5.) This is in accordance with the findings that at high altitudes the volume of the air breathed is increased and remains so after acclimatization has occurred. The increased volume of air breathed greatly diminishes the arterial anoxemia by diminishing the difference between the atmosphere and alveolar oxygen tension.

Hemoglobin Content

Paul Bert[24] (1878) suggested and later verified that the oxygen capacity of the blood was increased at high altitude. Viault[30] (1891) showed that the number of red blood cells and the oxygen content are increased at high altitudes. On the average the percentage of hemoglobin varies inversely with the barometric pressure and even quite small diminutions in the barometric pressure are effective in causing a rise in hemoglobin. It appears, therefore, that the hemoglobin is regulated in relation to the oxygen

Fig. 6.


HEMOGLOBIN IN GRAMS HGB./100 CC.
AS CALCULATED FROM TOTAL OXYGEN CAPACITY
GRAMS
30
20
10
0
1 HOUR IN TREADMILL
MEAN OF TWO DOGS
18.2
20.0
17.6
17.6
17.5
1½ HOURS IN TREADMILL
MEAN OF TWO DOGS
15.6
16.4
18.9
20.2
18.6
PNEUMONECTOMY
2 HOURS IN TREADMILL
MEAN OF TWO DOGS
13.6
15.1
15.2
16.8
18.6
MONTHS BEFORE 1
AFTER 2
3
4
5

pressure of the arterial blood and rises or falls accordingly as this pressure is diminished or decreased. The stimulus of the bone marrow by the state of anoxemia leads to a gradual increase in the total amount of hemoglobin in the body.

In connection with our experiments, it is interesting to note that there was a primary increase in the amount of hemoglobin in all animals following pneumonectomy, but that the hemoglobin returned to normal in those animals which had been run in the treadmill for only one hour, whereas the amount of hemoglobin continued to increase steadily after the primary rise in those animals which were run in the treadmill one and a half and two hours. (See chart #6). The fact that the one hour animals showed very little unsaturation of their arterial blood following exercise, whereas the one and a half and two hour animals showed considerable decrease in the saturation of the arterial blood may well account for the disparity. (See charts #1, #2, and #3.)

DISCUSSION AND SUMMARY

Review of the literature not only of experimental pneumonectomy, but of the physiologic changes following pneumonectomy reveals the fact that most of the observations have been limited to changes under resting conditions. Since it is only under conditions of actually increased tissue demands that the efficiency of the cardio-respiratory unit can be tested, it was decided to attempt to evaluate in accurate physiologic terms the degree of cardio-respiratory impairment following total pneumonectomy and to assay the degree to which the animals could in time achieve a functional adaptation to the anatomic removal of approximately 50% of their pulmonary tissue.

In order to do this a group of healthy young dogs were selected and trained. The physiologic response to varied amounts of moderate strain (1,1 1/2, 2 hours in the treadmill) and to the most severe strain (anoxemia test), were determined. In addition studies were made of the statics (subtidal lung volume) and dynamics (rate and depth and character and slope of the curve of respirations) of the respiratory apparatus. The hemoglobin was determined from the total oxygen capacity of arterial blood. In addition some studies were made of the oxygen debt.

The animals were then pneumonectomized, the left lung being removed by separate ligature of the vessels and closure of the bronchial stump with silk. An interval of two months was then allowed in order to assure the recovery of the animals to the point that they could bear up under the rigors of the tests. The above observations were then repeated at monthly intervals and the response to strain correlated with changes in tidal air, subtidal lung volume, hemoglobin, arterial oxygen saturation, etc.

The results of the exercise experiments may be summarized as follows: The one hour group showed a slight rise in temperature, pulse and respiration but did not show any unsaturation of the arterial blood after the run of 2300 meters. Following pneumonectomy the temperature elevation was doubled while the pulse acceleration was tripled. The respirations were slightly increased and there was but slight unsaturation of the arterial blood. There was a tendency for the temperature and pulse rises to return toward the pre-operative levels.

The one and a half hour group following the run of 3450 meters showed a moderate increase in the temperature, pulse and respiration, but they did not show any decrease in the saturation of the arterial blood. Following pneumonectomy they showed a more marked elevation of temperature, pulse and respiration and there was a marked decrease in the saturation of the arterial blood. On succeeding runs the degree of unsaturation markedly decreased. Clinically these animals showed much more embarrassment post-pneumonectomy than did the one hour group.

The two hour group after a run of 4600 meters showed a moderate increase in temperature, pulse and respirations along with a slight decrease of the saturation of the arterial blood. Following pneumonectomy the animals showed a very alarming elevation of the pulse and respiration associated with a very marked unsaturation of the arterial blood. On succeeding runs the animals showed less alarming elevation of pulse and respiration and considerably less unsaturation of the arterial blood, although these values never approximated the pre-operative levels. These experiments indicate that as the amount of strain is increased, the pneumonectomized animals show an increasing amount of embarrassment. In short, the cardio-respiratory reserve following pneumonectomy is still sufficient for resting conditions and for moderate exercise. But, as the amount of strain is increased, the impairment of cardio-respiratory reserve becomes increasingly more apparent. On succeeding runs months later there is a tendency for the animals to show increasingly less embarrassment, due to compensatory changes:- (1) The increase in the tidal air tends to diminish the difference of the oxygen tension between that of the atmospheric air and alveolar air. (2) The increased subtidal lung volume may increase functional diffusing area of the lungs. (3) The steady increase in hemoglobin bespeaks more effective carriage of the oxygen to the tissues with a tendency for the blood returning to the lungs to be less unsaturated.

In terms of ultimate strain on the cardio-respiratory unit by means of the anoxemia test, the critical level of oxygen for the normal animals before pneumonectomy showed a clear cut end point between five and six percent oxygen (average 5.6% oxygen). Following pneumonectomy, this value was found to have risen to practically double its previous value (11.3% oxygen). Four months after pneumonectomy, this level showed a tendency to drop slightly for all animals to approximately 9.0%. These findings suggest that with pneumonectomy the respiratory reserve is cut in half, due to the removal of practically 50% of the functional diffusing lung area. Within four months, however, after operation some readjustment is occurring whereby the animal can get by on a slightly lower oxygen tension. The nature of this compensatory mechanism is unknown at present. Whether it is on the basis of oxygen secretion (Haldane) or true pulmonary hyperplasia (Hilber) remains yet to be determined. To this end, studies are being made of changes in the relation of the oxygen tension of alveolar air to the oxygen tension of the arterial blood both before and after pneumonectomy. In addition, wax models are to be made of the microscopic structure of the remaining lung at various intervals following pneumonectomy and compared with similar wax models made of the normal lung (removed at the time of pneumonectomy).

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