STUDIES ON PULMONARY EDEMA

I. The Consequences of Bilateral Cervical Vagotomy in the Rabbit*†

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Plates 11 to 13

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During the past several years, we have been interested in the finding of acute pulmonary edema in a number of necropsies performed on patients who suffered from central nervous system disturbances with involvement of the brain stem. Since, in these instances, the usual explanations for the pathogenesis of pulmonary edema were inadequate, an investigation of the conditions obtaining in these patients was made. Certain clinical and pathologic observations, which will be described at another time, pointed to involvement of the nuclei of the vagus nerves. An experimental approach to the problem was therefore directed along that line. This report is intended as an introduction to a study of pulmonary edema of this type.

Materials and Methods

Healthy rabbits varying in weight from 800 to 2500 gm. were selected. A variety of anesthetics was employed. The most satisfactory was local skin infiltration with novocaine (1 per cent). Urethane and various barbiturates were also used, and were administered either intravenously or intraperitoneally. Moon (1) has pointed out in this connection that large doses of sodium phenobarbital cause shock and pulmonary edema, and has warned against its use in experiments dealing with the lungs. Control studies were carried out in our experiments with the various drugs employed. In no case, with the minimal necessary amounts

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used, was there observed any change in the lungs which could be confused with the pathologic alterations brought about by our experimental procedures. It may be mentioned that neither section of the depressor (aortic) nerves, which run as separate nerves in the rabbit, nor unilateral vagotomy (right or left) caused demonstrable changes in the lungs.

The vagus nerves were severed as low in the neck as was possible. It is evident that when bilateral cervical vagotomy is effected, the function of the recurrent laryngeal nerves is lost, and all vagal control below that level is abolished.

EXPERIMENTS

Series 1.—

Survival Time.—Following bilateral cervical vagotomy rabbits of 800 to 2500 gm. in weight died usually in from 8 to 24 hours. In exceptional cases, a survival time of from 36 to 62 hours was observed. It should be emphasized that death invariably occurred after bilateral vagotomy. In general, the older and heavier animals lived longer than the younger animals. It was impossible, even after a large experience, to predict the survival time of a rabbit with any greater accuracy than within 1 to 2 hours.

Clinical Picture.—Soon after vagotomy, the respirations became slower and deeper. After 2 to 3 hours, the respiratory rate increased appreciably. Restlessness was noticeable. Soon the respiratory movements became rapid and labored, and distinct râles could be heard. A period of increasing excitement with marked dyspnea then ensued, followed within a few minutes by a crisis in the animal's condition. Frothy serous fluid poured from the nose and mouth. In a number of instances, the fluid was frankly hemorrhagic in character. An immediate and striking change in the animal's condition was now noted. The animal was once more quiet, and respiratory movements were slower and less labored. At intervals, smaller amounts of frothy fluid were expelled from the mouth and nose. It appeared likely that some of the fluid came from the mouth and not all from the upper respiratory tract. Episodes similar to the first crisis occurred once or twice more before the animals died. Death finally occurred after a short period of great excitement and dyspnea, with bubbles of frothy fluid in the mouth and nose. The animals appeared to be drowning in the fluid in the respiratory tract.

Postmortem Findings.—Necropsies were conducted in each case, and without delay in the majority of the experiments. The most striking changes were restricted to the upper respiratory tract and the lungs. No evidences of ascites or pleural or pericardial effusion were found.

The larynx, trachea, and bronchi were filled with frothy serous or serosanguineous fluid, which poured freely over the cutting board. Their mucosal surfaces were injected, but no purulent exudate in the gross was found. Occasionally, but not in all experiments, small amounts of thick mucus and vomitus were present in the upper respiratory tract. In no case, however, was obstruction to the upper

respiratory tract demonstrable. The lungs were increased in size, and greatly increased in weight (Fig. 1). Rib markings were usually present on the posterior and lateral aspects of both lungs. The superficial lung tissue in both upper lobes was pink and overdistended. All remaining portions of both lungs were heavy, solid, and airless. The visceral pleura was stretched taut over these areas. On section, the lung surfaces in the involved portions were deep red to red-black in color, and completely consolidated. Frothy fluid could be expressed from the lung parenchyma. The vessels were engorged, and the tissues, in general, markedly congested. All branches of the upper respiratory tract and the bronchial system appeared to be dilated, although a precise standard of comparison is not at hand. Moderate dilatation of the right auricle and right ventricle was present. Fluid blood was usually found in the heart chambers. If the autopsy was delayed for a short time after death, postmortem clots were generally found in the heart. Changes in the other organs have no bearing on this report, and will not be described at this time.

On microscopic examination, no significant changes were noted in the heart. The mucosal surfaces of the larynx and trachea showed occasional acute inflammatory changes. The submucosal veins and capillaries were enormously distended with blood. In the lungs, variable amounts of pneumonic exudate, consisting chiefly of neutrophiles and eosinophiles, were scattered throughout the involved areas, particularly in the lungs of those rabbits which survived longer than 18 hours. Occasional evidences of aspiration of food and vomitus were also present. Desquamated cells from the pharynx, mouth, and upper respiratory tract could be recognized in scattered areas. By far the most important change in the lungs, however, was the massive pulmonary edema, which involved not only the air spaces and bronchioles, but the interstitial tissues as well (Fig. 2). The air spaces were filled with precipitated pale eosinophilic albuminoid material, in which air bubbles were frequently entrapped. In some areas numerous hyaline membranes[1] composed of deeply staining concentrated albuminoid material lined the walls of alveoli and alveolar ducts (Fig. 3). In some instances, large areas of lung parenchyma were filled with red blood cells and serum.

The interstitial tissues were more prominent than usual, and their components were separated as by edema fluid. This was particularly true of the walls of the veins and arterioles. The perivascular lymphatics were greatly distended and filled with serum (Fig. 4). All veins and capillaries exhibited extreme degrees of

[1] Wolbach (2) called attention to the presence of hyaline membranes in the lungs of patients who died during the last influenza epidemic and explained the pathogenesis of the membranes. Similar membranes may be found in a variety of conditions. Their presence is indicative of partial obstruction to respiration caused by fluid, plasma, exudate, or foreign materials of any kind in the lungs (Farber and Wilson, 3). In the experiments described above, the hyaline membranes are composed of albuminoid materials derived from the blood plasma.

distention (Fig. 5). The alveolar wall capillaries projected into alveolar spaces. The arterioles were also dilated, but were not as markedly involved as the veins.

The emphysematous areas, observed on gross examination, extended but a short distance beneath the pleura. Thinning of the walls and increase in size of the alveoli were the only noteworthy features in these areas.[2]

The chief gross and microscopic findings in rabbits which die after bilateral cervical vagotomy are therefore: (*a*) severe acute pulmonary edema and congestion; (*b*) variable amounts of acute bronchopneumonia; (*c*) evidences of aspiration of food and secretions; (*d*) terminal dilatation of the right side of the heart.

The postmortem findings in the lungs of rabbits which die after bilateral cervical vagotomy, are similar to those in certain diseases of the central nervous system, with involvement of the brain stem, such as the bulbar form of poliomyeloencephalitis. Certain clinical features, common to both the experimental animals and the human patients, strongly suggest a common pathogenesis.

There is a voluminous literature on the subject of bilateral cervical vagotomy. No review will be attempted here for adequate accounts are obtainable in the collected papers of Schiff, 1894 (4), the monograph of Frey, 1877 (5), and the more recent writings of Schafer (6). It is of interest that experiments concerned with the effects of double cervical vagotomy were mentioned by Galen, and Legallois (7), 1812, gives the history of such experiments from the time of Rufus of Ephesus, a Greek physician who lived in the reign of Trajan.

There is no agreement in the literature concerning the pathologic findings, the pathogenesis of the pulmonary changes, or the cause of death following bilateral cervical vagotomy. A vast amount of work based on ingenious experiments was carried out, particularly during the last century, and many observations which hold true today were made on the function of the vagus and its branches. The most impressive papers are those of Schiff. There are certain obvious explanations for the divergent conclusions defended by the most active workers: observations often were not extended long enough, secondary infections played too

[2] The best results in the histologic demonstration of pulmonary edema were obtained when the lungs were fixed *in toto* in adequate amounts of 10 per cent formalin solution, or when thick sections of lung were so preserved. Thin sections were selected after several days. Placing of the bottles containing the fresh tissue in the incubator at a temperature of 52°C. for several hours, to aid in the precipitation of the edema fluid, is also of value, but is not a necessary procedure. Poor results were obtained when thin fresh sections of lung were fixed in Zenker's solution or in 10 per cent formalin solution.

important a rôle, and the age of the animal is of importance, since the less rigid laryngeal cartilages in very young animals permits laryngeal obstructions to occur more easily than in older animals. Furthermore, it is possible that not all types of animals behave in the same way; conditions in the cat and the dog may differ from those in the rabbit and guinea pig in important respects. No discussion of these differences will be attempted at this time. This paper is confined to the results of experiments on the rabbit.

The conclusions as given in the literature on this subject may be summarized. Death occurs after bilateral cervical vagotomy because of: (*a*) Aspiration pneumonia (vagus pneumonia); as a consequence of laryngeal paralysis, mouth secretions and food are aspirated causing an acute lobular pneumonia (Traube, 8, Frey, and others). (*b*) Slow asphyxia, secondary to laryngeal paralysis. With inspiration there is falling together of the thyro-arytenoid ligaments and the arytenoid cartilages (Legallois, Schafer). (*c*) Neuroparalytic pulmonary congestion, as a consequence of a loss of the tonic vasoconstrictor action of the vagosympathetic nerves (Schiff).

Our clinical and pathologic studies on the rabbit have disclosed the existence of a fourth factor to account for the pulmonary changes and death following bilateral cervical vagotomy. Asphyxia caused by the gradually increasing pulmonary edema serves to increase the severity of the pulmonary edema. The intense dyspnea, the frothy fluid in the upper air passages, and the hyaline membranes, entrapped air bubbles, and large amounts of fluid in the lungs on microscopic examination, are evidences of this. It is known that asphyxia causes dilatation of capillaries (Krogh, 9) and increases the permeability of capillaries (Landis, 10), factors which lead to pulmonary edema.

Since the pulmonary edema and congestion were of such marked degree, it appeared worthwhile to study the mechanism of their production with the factors mentioned above in mind. The first two conditions making for the fatal outcome result from the laryngeal paralysis that occurs when both vagus nerves are severed in the neck. In an extensive experience in the experimental study of slow asphyxia in animals, pulmonary edema of such severity as was observed in the present experiments was never encountered, an observation not in harmony with the theory of Schafer. The laryngeal factor can be excluded by the use of a tracheotomy tube. This method was used in a second series of experiments on rabbits.

Series 2.—

Rabbits were prepared as before, except that a cannula of suitable size was inserted into the trachea before a bilateral cervical vagotomy was performed. The trachea above the cannula was ligated, and in a number of experiments, the esophagus at the level of the tube was also ligated. Suitable control experiments were performed on rabbits equipped with tracheal cannulae. The vagus nerves were not sectioned. Such control animals were kept alive for a period of 24 hours longer than the usual survival time observed after bilateral cervical vagotomy. No pulmonary edema was found in postmortem examination performed when these animals were sacrificed.[3] It is of greatest importance to keep the tracheal cannula clean and free from obstruction. The patency of the cannula was always tested at necropsy.

In a series of rabbits prepared with tracheal cannulae, both vagus nerves were severed in the neck, as in series 1. All animals died. When litter mates were used, one with a cannula, and one without, the animal with a cannula survived approximately 20 per cent longer than the one without. Comparison of the survival time of the entire group in series 2 (with tracheal cannulae) with that of series 1, shows that if the factor of laryngeal paralysis is excluded, the survival time, which varied from 10 to 26 hours, is increased. The clinical picture was, in general, the same as in series 1, except for a somewhat later onset of dyspnea. It was of interest that even though the esophagus and the trachea above the cannula were tied, small amounts of fluid dropped from the nose and mouth during the last hour or two before death. An accumulation of secretions in the mouth is also a part of the picture produced by bilateral cervical vagotomy. The chief pathologic findings were acute pulmonary edema and congestion of about the same order of severity as in series 1. The gross and microscopic pictures were similar to those in the animals without cannulae. The chief differences were that no evidences of aspiration of food or mouth secretions, or of bronchopneumonia, were present.

DISCUSSION

We can conclude that the laryngeal paralysis, incidental to section of both vagus nerves in the neck, is not essential to the production of the severe pulmonary edema which follows bilateral cervical vagotomy in the rabbit. The observation that rabbits die after bilateral cervical vagotomy even when equipped with tracheal cannulae is in agreement with the reports of Schiff and others. The conclusions of a number of workers (Traube, Frey) to the contrary are not understandable in the light of our own experiments.

[3] The best method for causing immediate death was the injection into the cisterna magna of the rabbit of a few cubic centimeters of 1 per cent novocaine. Death occurs instantaneously. Confusing pulmonary changes are thus avoided.

In considering the results of the experiments performed in series 2, emphasis may be placed upon the production of severe pulmonary edema and congestion under conditions which permit the exclusion of infection, aspiration of foreign materials, and slow asphyxia. To denote the pathogenesis of this type of pulmonary edema, the term neuropathic pulmonary edema will be employed. Further studies concerning the pathogenesis of this type of pulmonary edema will be reported.

CONCLUSIONS

1. Bilateral cervical vagotomy in rabbits soon leads to death, usually within 8 to 24 hours.

2. Gradually increasing dyspnea, crises with expulsion of frothy, serous or sanguineous fluid from the mouth and nose, and terminal asphyxia are the important clinical features.

3. Postmortem examination reveals severe acute pulmonary edema and congestion, variable amounts of bronchopneumonia, and evidences of aspiration of food and secretions. This picture is similar to that found in the lungs in the bulbar form of poliomyelitis.

4. These changes are brought about by a combination of factors secondary to bilateral vagotomy: laryngeal paralysis (aspiration of food, slow asphyxia); loss of the vagal innervation of the lungs.

5. Laryngeal paralysis is not an essential factor in the production of severe pulmonary edema and death following bilateral cervical vagotomy.

6. To denote the pathogenesis of this type of edema, the term neuropathic pulmonary edema is employed.

BIBLIOGRAPHY

1. Moon, V. H., and Morgan, D. R., *Arch. Path.*, 1936, **21**, 565.
2. Wolbach, S. B., *Bull. Johns Hopkins Hosp.*, 1919, **30**, 104.
3. Farber, S., and Wilson, J. L., *Arch. Path.*, 1932, **14**, 437.
4. Schiff, M., Gesammelte Beitraege zur Physiologie, Lausanne, B. Benda, 1894, **1**.
5. Frey, O., Die pathologischen Lungenveraenderungen nach Laehmung der Nervi Vagi, Leipsic, Wilhelm Engelmann, 1877.
6. Schafer, E. S., *Quart. J. Exp. Physiol.*, 1919, **12**, 231.
7. Legallois, M., Experiments on the principle of life, Philadelphia, M. Thomas, 1813.

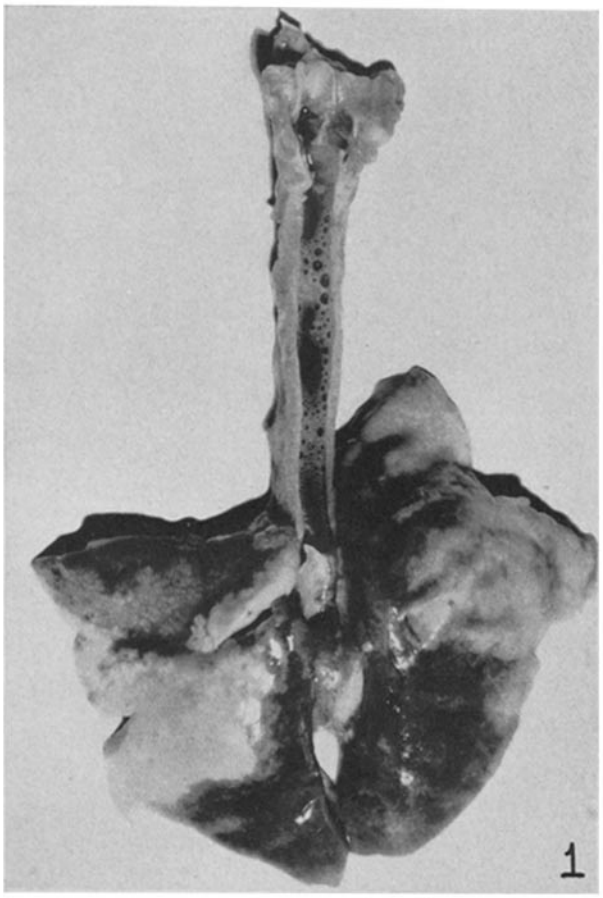
8. Traube, L., Gesammelte Beitraege zur Pathologie und Physiologie, Berlin, August Hirschwald, 1871.
9. Krogh, A., Anatomy and physiology of capillaries, New Haven, Yale University Press, 2nd edition, 1929.
10. Landis, E. M., *Physiol. Rev.*, 1934, **14**, 404.

EXPLANATION OF PLATES

PLATE 11

FIG. 1. Photograph of lungs and opened trachea of rabbit which died 25 hours after bilateral vagotomy. The dark portions are consolidated because of intense congestion and edema. Superficial emphysema is present in the pale areas. The trachea is filled with fluid containing air bubbles.

We are grateful to Dr. Orville T. Bailey for the photomicrographs.

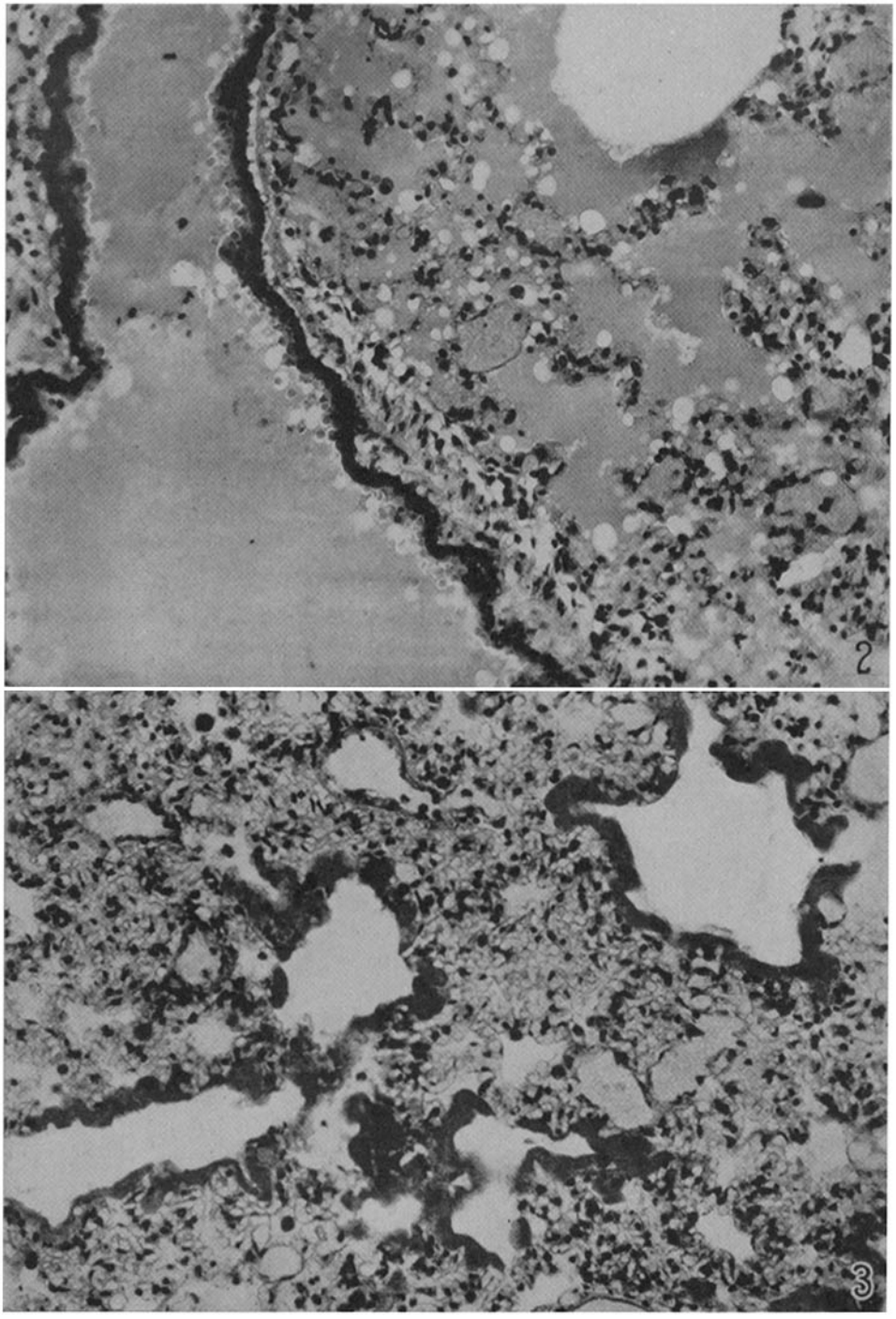


(Farber: Pulmonary edema. I)

PLATE 12

FIG. 2. Photomicrograph of lung of rabbit which died as a result of bilateral cervical vagotomy. The bronchiole and alveolar spaces are filled with edema fluid in which numerous small air bubbles are entrapped. Note great dilatation of alveolar wall capillary near center of picture. Hematoxylin and eosin. Reduced from a magnification of 300 diameters.

FIG. 3. Photomicrograph of lung of rabbit which died as a result of bilateral cervical vagotomy. Note the hyaline membranes composed of materials derived from the blood plasma lining the walls of alveoli and alveolar ducts. The capillaries are greatly distended. Hematoxylin and eosin. Reduced from a magnification of 300 diameters.

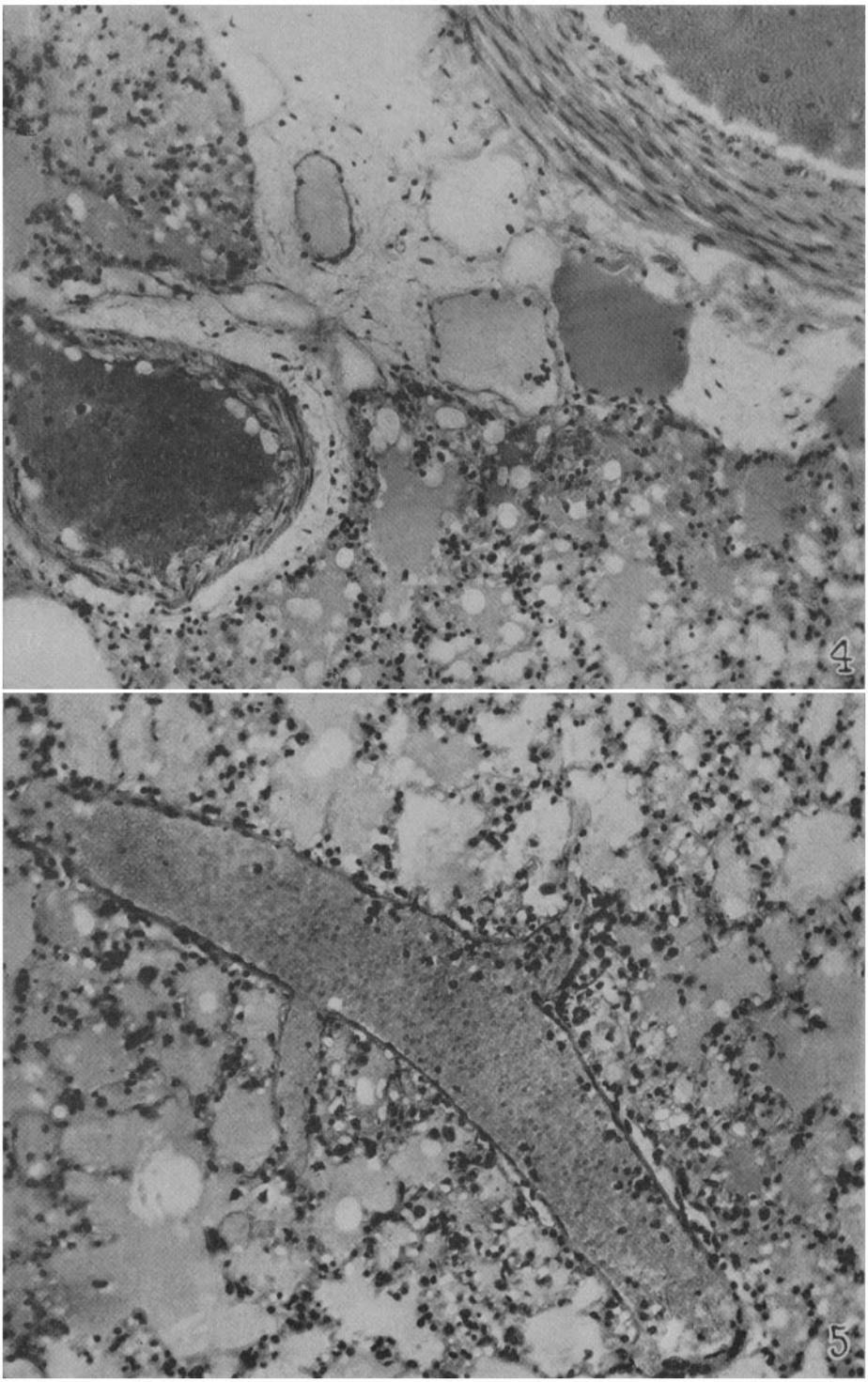


(Farber: Pulmonary edema. I)

PLATE 13

FIG. 4. Photomicrograph of lung of rabbit which died as a result of bilateral cervical vagotomy. Note edema of periarterial tissues and dilatation of lymphatics which were filled with serum. The air spaces are filled with fluid and entrapped air. Hematoxylin and eosin. Reduced from a magnification of 250 diameters.

FIG. 5. Photomicrograph of lung of rabbit which died as a result of bilateral cervical vagotomy. Note great dilatation of a small vein. The surrounding air spaces are filled with edema fluid. Hematoxylin and eosin. Reduced from a magnification of 250 diameters.



(Farber: Pulmonary edema. I)