# LUNG EDEMA FOLLOWING BILATERAL VAGOTOMY

## Studies on the Rat, Guinea Pig, and Rabbit

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(Received for publication, May 26, 1939)

The association clinically of organic central nervous system disease and pulmonary edema invites inquiry regarding the rôle of the vasomotor nerves to the lungs in the pathogenesis of pulmonary edema.

Vasoconstrictor action of the vagus fibers to the lung has been described in the isolated, perfused organ of the rabbit and guinea pig (1, 2). Under similar conditions in the rat's lung, acetyl choline has been shown to have the same effect (3). Weiser (4) sectioned both vagi in rats, producing death in a few hours, with marked hyperemia and edema of the lungs. Unilateral vagotomy resulted in an increased permeability of the organ on the operated side to colloidal dye introduced into the trachea after death. Findings in the bilaterally vagotomized animals were accounted for on the basis of a permeability change plus hyperemia resulting from section of both vagi. Laryngeal obstruction following this procedure was dismissed as unimportant. A report of pulmonary edema developing within 30 minutes following instrumentation of the lower esophagus appears in the literature (5). Postmortem examination revealed both vagi involved in carcinomatous metastases near the cardia. The edema was ascribed to trauma to the vagi, on the basis of Weiser's (4) experimental findings.

More recently, Farber (6) has investigated the effect of bilateral vagotomy in the rabbit and guinea pig, cannulating the trachea to rule out the effect of laryngeal obstruction. In addition, in the guinea pig, artificial respiration was given. All animals invariably died, the guinea pigs within about 4 hours, and the rabbits after a somewhat longer time. The clinical course, as observed in the rabbit, was marked by periods of increasing dyspnea, followed by crises during which foam poured from the mouth. In both species of animal the chief finding at postmortem examination was massive pulmonary edema and congestion. Cocaine-soaked pledgets applied to the roots of the lungs in guinea pigs produced the same results. With the sternum raised, the heart was observed to beat regularly even after extensive pulmonary change had already occurred. The author concluded that interruption of the vagal fibers to the lung, in the rabbit and guinea pig, results rapidly in death due to a neuropathic pulmonary edema. The relatively heavy muscular coat found in the walls of the pulmonary arteries and arterioles of these animals (7) contributes to the plausibility of this conclusion.

The status of the other common laboratory animals in this regard is a matter of some interest. Schafer (8), by first cauterizing the thyro-arytenoid ligaments, was able to keep cats alive several months following bilateral vagotomy. He reported that the

congestion and edema seen in the lungs of animals dying after bilateral vagotomy was similar to that seen in slow asphyxia with the vagi intact. Boothby and Shamoff (9) reported that dogs in which all branches of the vagi between the recurrent laryngeal nerves and the two primary gastro-intestinal branches were divided did well even if both sides were operated upon at the same time. Pavlov's (10) dogs survived if only one vagus was cut below the recurrent laryngeal, the other being separated in the neck. In view of the foregoing, it can be stated with certainty that the cat and dog can survive in the absence of vagal innervation to the lungs.

In the following studies this question was reinvestigated in the rat, guinea pig, and rabbit, in an effort to determine the basis for the differences reported in the different species.

Before going into the experimental results it would be well to consider briefly the concept of a lung edema produced by the action of nerve endings directly on the vessels of the lung. This could be brought about either by a change in permeability, a local circulatory change favoring transudation, or both. There is no evidence that in the living mammal the vasomotor nerve can affect specifically the permeability of the vessel which it innervates (11, 12). The only local circulatory change in the lung that can be postulated for bilateral vagotomy is an active hyperemia. This condition may or may not effect an increase in filtration, depending upon the extent to which it influences capillary pressure, but alone it has not been found capable of producing edema (12, 13). It may be argued that studies carried out on other capillary beds need not necessarily apply to the pulmonary vessels, since here the unique structure of the tissue renders it particularly liable to edema. In this connection the studies of Gibbs (14) are of interest. This investigator found that in the presence of general edema-forming conditions (plethora, universal capillary damage), edema appears first and most markedly in the superficial tissues of the head and neck, and while pronounced edema may be widespread, the lungs are only slightly involved or not at all. It seems probable, therefore, that the effects of active hyperemia are at least no more drastic in the lung than elsewhere, and perhaps less so, when the location of the pulmonary capillary bed behind the left ventricle is considered. While the heart continues to beat vigorously and respond sensitively to changes in venous pressure, it is unlikely that a hyperemia resulting from denervation of the lungs can cause a significant increase in pulmonary capillary pressure. Therefore, unless the vagus exerts a specific, and as yet unknown, effect on the permeability of the lung capillaries, it appears that the changes described by Farber (6) cannot be explained simply by the loss of vasomotor control of the lung vessels, and that one might anticipate much the same reaction to bilateral

vagotomy from the smaller as from the larger species of laboratory animal, in this particular respect.

## *Methods*

Adult rats, guinea pigs, and rabbits were used in these studies. Most surgical procedures were carried out under nembutal anesthesia administered intraperitoneally in doses varying from 20 to 35 mg. per kilo, depending upon the depth of anesthesia needed for the particular procedure. In a few experiments a light initial ether anesthesia was combined with procaine infiltration, and in some, small doses of nembutal were used together with local infiltration. In experiments in which the animals were immobilized for a number of hours, light anesthesia was maintained with small doses of nembutal given as needed.

Bilateral cervical vagotomy with and without tracheotomy, bilateral section of the recurrent laryngeal nerves with and without vagotomy, and bilateral vagotomy in two stages, sparing the recurrent laryngeal nerve on the right side, were undertaken in a large number of animals. Some of these procedures will be described in detail in connection with the experimental observations.

The clinical course of all animals was followed closely. In those with an open trachea, patency of the lumen was frequently checked. With the head well extended, gentle traction on the distal segment of the trachea and transillumination gave good visualization of the lumen for some distance. In animals with a closed trachea in which visualization of the larynx was of interest, direct laryngoscopy was carried out, using a glass tube of suitable diameter introduced into the pharynx. Transillumination or direct light served equally well. The nature, rate, and sounds of respiration were carefully noted throughout, as well as the character of the material found in the respiratory passages. In the larger animals auscultation of the lung areas was employed.

Animals subjected to simple tracheotomy were immobilized on their backs throughout the course of the experiment to permit proper care of the wound. In these cases suitable precautions were taken to conserve body heat. In a number of such experiments air warmed to 37°C. and saturated with water vapor was supplied to the animal. This was discontinued when its negative value, under the particular circumstances, was amply demonstrated.

Routine necropsy was done immediately after death. Tissues taken for microscopic examination were placed in 10 per cent formalin at once.

## *Bilateral Vagotomy in the Rat*

In four albino rats the vagi were separated low in the neck under ether and procaine anesthesia. Death resulted within 2 hours in each case, the clinical course being characterized by marked dyspnea and a harsh inspiratory crow, both appearing immediately after vagotomy and persisting till death.

At postmortem examination the presence of variable amounts of viscid mucus in the larynx, trachea, and bronchi was a constant finding, while froth appeared in the respiratory passages in one animal. The lungs

exhibited extensive, dark red-purple, atelectatic areas, the cut surfaces yielding a moderate to copious flow of sanguinous froth. Moderate right heart dilatation, a large dark liver, and congested systemic veins were uniformly noted. These experiments confirm the observations of previous workers.

### *Bilateral Vagotomy with Tracheotomy in the Rat*

Attempts to develop a suitable technique for tracheotomy were next made, in order to eliminate the laryngeal obstruction produced by bilateral cervical vagotomy.

In a series of eleven control animals the trachea was cannulated, the vagi being left intact. The flow of secretion induced by the "foreign body" in the trachea made it impossible to maintain an adequate airway for much more than 12 hours. In those animals in which a high degree of obstruction had been present for a number of hours, the changes in the lungs following intubation approximated those just described in the vagotomized animals.

A satisfactory method for the ends desired proved to be simple tracheotomy. The muscles overlying the trachea were split in the midline and retracted by loose ligatures passed laterally through the skin. The trachea, without the dissection and handling necessary in cannulation, was opened by a small transverse slit. The procedure was carried out under nembutal anesthesia administered intraperitoneally, and given in small repeated doses throughout the duration of the experiment to prevent struggle, since it was necessary to keep the animals fixed on their backs in order to take proper care of the wound. Thus a free air-way could be maintained in a high percentage of cases. In a number of animals, however, considerable quantities of viscid mucus were found on opening the trachea at the very outset. In such experiments evidence of respiratory obstruction frequently appeared after several hours, although the material found in the trachea initially had been removed as completely as possible. Operating a few minutes after anesthetizing the animal, and the additional simple expedient of elevating the hind quarters, served to minimize this difficulty.

Bilateral cervical vagotomy was done in fifteen rats tracheotomized as described. Eight animals in which evidence of obstruction was either minimal or absent were sacrificed at intervals ranging from 6 to 21 hours from the time of operation. Gross examination revealed small amounts of viscid mucus in the air passages. The lungs showed small areas of pale, gray-purple mottling posteriorly, a finding seen in the control animals. Other organs were entirely normal. Microscopic examination of the lungs showed areas of slight to moderate congestion comparable in extent to those found in control specimens with simple tracheotomy and vagi intact. Alveolar exudate was lacking.

Observations on those animals of this series that developed evidence of respiratory obstruction are of some interest. A fine, cotton-tipped wire applicator passed gently into the trachea could, in most cases, at least partially dislodge the tenacious secretion causing the obstruction, with immediate clinical relief. The longer the obstruction was permitted to remain, the less symptomatic improvement resulted from its removal. Animals sacrificed from 10 minutes to over an hour after the first signs of obstruction showed pulmonary changes ranging from small areas of moderate congestion in the 10-

minute specimen, to widespread engorgement with exudate in the alveoli, in the longest survival. At the onset of obstructive symptoms, transillumination of the trachea and inspection of the lumen frequently revealed a ring of thick mucus decreasing considerably the diameter of the air-way. When the trachea was opened, the secretions formed a thin coat closely adherent to the wall, so that a postmortem examination alone could give no idea of the extent of the barrier formed by this material. Table I summarizes the observations in experiments of this group.

From these experiments it was seen that if a free air-way was not maintained changes occurred in the lungs which ultimately became irreversible. Subsequent efforts to clear the trachea offered no relief, death regularly following a period of marked dyspnea. Postmortem examination could reveal no clear cut evidence of obstruction. Therefore, in the absence of the antemortem observations described, it might have mistakenly appeared that vagotomy was entirely responsible for the changes noted.

There appeared to be a difference, however, between the intact and vagotomized animal's response to respiratory obstruction. The following experiments were done to establish this point with greater certainty.

### *Section of the Recurrent Laryngeal Nerves in Rats with Intact Vagi*

Section of the recurrent laryngeal nerves was chosen as a simple means of comparing the effects of respiratory obstruction in the intact rat and the vagotomized animal. The marked pulmonary changes found in animals that have undergone bilateral section of the vagi above the recurrent laryngeal nerves, without tracheotomy, have already been described.

In six albino rats the recurrent laryngeal nerves alone were severed in the neck. Direct inspection of the glottis in these and the vagotomized animals revealed the vocal cords lying in close approximation, the air-way being uniformly reduced to a small slit. Dyspnea and stridor were of equal intensity in both series. However, animals with intact vagi sacrificed after several hours exhibited only limited areas of moderate to marked pulmonary congestion, while others that were allowed, lived for many days, pneumonic consolidation dominating the pathologic picture at death. Dyspnea remained a prominent part of the clinical picture throughout, though not as intense as immediately after cutting the recurrent laryngeal nerves. In animals in which the vagi were cut a day or two after separation of the laryngeal nerves, death resulted promptly within a few hours, the lung findings paralleling those already described for bilaterally vagotomized animals without tracheotomy. Table II summarizes the results of these experiments.

### *Right Sided Vagotomy below the Recurrent Laryngeal Nerve, with Left Sided Cervical Vagotomy, in the Rat, Guinea Pig, and Rabbit*

In an effort to establish prolonged survival in animals deprived of vagal innervation to the lungs, five albino rats were vagotomized in two stages.

TABLE I

*Rats with Tracheotomy; Bilateral Vagotomy and Tracheotomy*

| No. | Sex | Weight | Anesthesia | Procedure | Clinical course | Survival | Pathology |
|---|---|---|---|---|---|---|---|
| | | *gm.* | | | | | |
| F | M | 350 | Ether and procaine | Trachea cannulated, vagi intact | Progressive dyspnea, termination in asphyxial convulsions | 2½ hrs., death spontaneous | Lungs: Distended and hyperemic. Small scattered areas of moderate to marked congestion<br>Respiratory passages: Cannula plugged with thick mucus. Small amount of serous fluid in trachea and bronchi |
| G | M | 270 | " " | " " | " " | 3¾ hrs., death spontaneous | Lungs: Distended and hyperemic. Small scattered areas of moderate to marked congestion, confluent in some regions<br>Respiratory passages: As in (F) |
| H | M | 380 | " " | " " | " " | 16 hrs., death spontaneous | Lungs: Hyperemic. Extensive areas of marked congestion and edema<br>Respiratory passages: As in (F) |
| I | M | 320 | " " | " " | " " | 4 hrs., death spontaneous | Lungs: As in (G)<br>Respiratory passages: As in (F) |
| Q | M | 250 | Nembutal | " " | Respiratory efforts not as forceful as animals operated under local anesthesia | 5 hrs., death spontaneous | Lungs: Distended and hyperemic. Small scattered areas of slight to moderate congestion<br>Respiratory passages: As in (F) |
| V | M | 150 | " | Tracheotomy without cannulation, vagi intact | Thick mucus removed from trachea at intervals. Otherwise uneventful | 12 hrs., sacrificed | Lungs: Small scattered areas of slight congestion<br>Respiratory passages: Small amounts of viscid mucus in trachea and bronchi |
| W | M | 175 | " | " " | " " | " " | As in (V) |
| Z | M | 250 | " | " " | " " | " " | " " " |
| 1 | F | 200 | " | Tracheotomy and bilateral vagotomy | Course uneventful except for evidence of respiratory obstruction appearing 10 min. before death | 6 hrs., sacrificed | Lungs: Scattered areas of moderate engorgement<br>Respiratory passages: As in (V) |

TABLE I—*Concluded*

| No. | Sex | Weight | Anesthesia | Procedure | Clinical course | Survival | Pathology |
|---|---|---|---|---|---|---|---|
| | | *gm.* | | | | | |
| 4 | F | 200 | Nembutal | Tracheotomy and bilateral vagotomy | Course uneventful, respiratory obstruction noted 30 min. before death | 4 hrs., sacrificed | Lungs: Moderately to markedly congested, for most part. Few small areas of exudate<br>Respiratory passages: As in (V) |
| 2 | F | 200 | " | " " | Course uneventful, respiratory obstruction noted 60 min. before death | 5 hrs., death spontaneous | Lungs: Extensive areas of marked congestion and edema<br>Respiratory passages: Small amount of viscid mucus and froth in trachea and bronchi |
| 3 | F | 200 | " | " " | No evidence of respiratory obstruction | 10 hrs., sacrificed | Lungs: Small, scattered. areas of slight to moderate congestion<br>Respiratory passages: Small amounts of viscid mucus in trachea and bronchi |
| 11 | F | 200 | " | " " | " " | 12 hrs., sacrificed | Lungs: Small areas of moderate to marked congestion<br>Respiratory passages: As in (3) |
| 12 | F | 200 | " | " " | " " | " " | Lungs: Small, scattered areas of slight congestion<br>Respiratory passages: As in (3) |
| 13 | F | 200 | " | " " | " " | " " | Lungs: Infrequent, scattered areas of slight congestion<br>Respiratory passages: As in (3) |
| 14 | F | 200 | " | " " | " " | " " | " " |
| T | M | 150 | " | " " | Thick mucus removed from trachea at intervals during latter part of course | 21 hrs., sacrificed | Lungs: Scattered areas of slight to marked congestion<br>Respiratory passages: As in (3) |

The above are representative samples from a larger series.

Under nembutal anesthesia, through a midline incision, the sternoclavicular joint was separated and the clavicle reflected laterally. Resection of the first rib and retraction of the second exposed the vagus beyond the origin of the recurrent laryngeal nerve, where it was cut. The intact recurrent laryngeal branch was visualized in each case before closure, and, in addition, the success of the procedure was checked postopera-

tively by direct inspection of the larynx. In a number of cases the excursions of the right vocal cord appeared slightly damped, the paresis probably resulting from handling of the vagus above the exit of the recurrent laryngeal nerve. For this reason, the second stage was not undertaken until 10 to 14 days later, at which time the left vagus was cut

TABLE II

*Rats with Recurrent Laryngeal Nerves Cut*

| No. | Sex | Weight | Anesthesia | Procedure | Clinical course | Survival | Pathology |
|---|---|---|---|---|---|---|---|
| | | *gm.* | | | | | |
| 1 | M | 250 | Nembutal and procaine | Recurrent laryngeal nerves cut | Marked dyspnea and stridor | 6 hrs., sacrificed | Lungs: Hyperemic. Scattered areas of moderate to marked congestion<br>Respiratory passages: Large amounts of viscid mucus in larynx and trachea |
| 2 | M | 250 | " " | " " | " " | 12 hrs., sacrificed | " " |
| 3 | M | 300 | " " | " "<br>Vagi cut after 24 hrs. | " " | Death spontaneous 3 hrs. after vagotomy | Lungs: Areas of marked congestion and edema<br>Respiratory passages: Moderate amounts of viscid mucus and froth in larynx and trachea |
| 4 | M | 250 | " " | Recurrent laryngeal nerves cut. Vagi cut after 48 hrs. | " "<br>Stridor less marked on 2nd day | Death spontaneous 3½ hrs. after vagotomy | Lungs: Areas of marked congestion and edema, as well as pneumonic consolidation<br>Respiratory passages: As in (3) |
| 5 and 6 | F | 150 | " " | Recurrent laryngeal nerves cut | Marked dyspnea and stridor. Stridor less marked after 1st day | Death spontaneous on 5th day (5) and 7th day (6) | Lungs: Extensive areas of congestion and pneumonic consolidation<br>Respiratory passages: Moderate amount of thick mucus in larynx and trachea |

in the neck, the right vocal cord having by this time recovered its function. Laryngoscopy following the second stage revealed the left cord immobilized in the midline, the right nearly meeting it during expiration. Tracheobronchial secretions accumulating behind this barrier produced a progressively increasing dyspnea.

The best survival reached 30 hours, the lungs at postmortem exhibiting extensive areas of intense congestion and exudate, as well as pneumonic consolidation. In one animal in which laryngofissure was done in an effort to provide exit for the accumulated secretions, the nature of the laryngeal and tracheal contents could be observed from time

to time during the 30 hours that the animal survived. A viscid mucus was always present. At no time was the frothy exudate characteristic of a pulmonary edema in evidence.

Nine guinea pigs were prepared as described in the experiments on the rat, except that the first rib was not resected. Survival ranged from 19 hours to 22 days. Intermittent periods of laryngeal obstruction characterized the clinical course of those animals that succumbed shortly after operation. In those that survived more than one day this was either not present or appeared only on exertion or excitement, dyspnea and diminished activity becoming evident prior to death. Postmortem examination revealed pneumonic consolidation to be the predominant change. The clinical picture was at no time that of a pulmonary edema. Three animals of this series in which laryngeal obstruction was minimal or wanting were sacrificed at 24, 36, and 48 hours after operation. The lungs in these animals were essentially negative.

Three rabbits were submitted to the same procedure. It was unnecessary to disturb the clavicle in these animals. Two of the three rabbits lived one day, the course and necropsy findings being similar to those noted in the guinea pigs exhibiting similar survival times. One animal lived 10 days, succumbing eventually to a pneumonia. Physical signs of lung edema were wanting throughout, the animal being alert and symptom-free till the day before death, the only abnormal finding being a laryngeal stridor induced by exertion or excitement. Table III presents these experiments in summary.

Studies similar to the first two groups done on the rat were also carried out on a much smaller series of guinea pigs. These yielded results less complete, but pointing in the same general direction.

## DISCUSSION

Without reflection on the possibility of a neuropathic pulmonary edema, the observations reported here make it unlikely that such a factor underlies the type of experimental result obtained by Farber (6) and Weiser (4). They would seem to indicate, rather, that obstructive asphyxia plays the dominant rôle, while loss of vagal innervation of the lungs is of no more than secondary importance. When the extensive changes in the lungs of rats that have died as little as one hour after bilateral vagotomy are contrasted with the minimal changes noted 12 and more hours after the same procedure in animals with successful tracheotomy, the importance of the laryngeal obstruction occurring in the first group becomes clear. The common

TABLE III

*Animals with Two-Stage Vagotomy, Sparing the Right Recurrent Laryngeal Nerve*

| No. | Sex | Weight | Anesthesia | Clinical course | Survival | Pathology |
|---|---|---|---|---|---|---|
| | | *gm.* | | | | |
| Rat 1 | F | 200 | Nembutal | Increasing respiratory obstruction | 30 hrs. | Lungs: Extensive areas of marked congestion and edema. Areas of pneumonic consolidation<br>Respiratory passages: Much viscid mucus in larynx and trachea. Small amount of serous froth |
| Rat 2 | M | 200 | " | Much viscid mucus removed at intervals through fissure in larynx | 30½ hrs. | " " |
| Rat 3 | M | 300 | " | Increasing respiratory obstruction | 23 hrs. | " " |
| Rat 4 | M | 200 | " | " " | 24 hrs. | " " |
| Rat 5 | F | 175 | " | " " | 19 hrs. | " " |
| Guinea pig 1 | M | 300 | " | Dyspnea and stridor on exertion | 22 days | Lungs: Areas of pneumonic consolidation<br>Respiratory passages: Negative |
| Guinea pig 2 | M | 300 | " | Dyspnea and stridor at intervals throughout course | 24 hrs. | Lungs: Areas of marked congestion, and of pneumonic consolidation<br>Respiratory passages: Small amount of viscid mucus in larynx and trachea |
| Guinea pig 3 | M | 300 | " | " " | 19 hrs. | " " |
| Guinea pig 4 | F | 250 | " | Respiration labored for several hours prior to death | 48 hrs. | Lungs: Extensive areas of pneumonic consolidation<br>Respiratory passages: Negative |
| Guinea pig 5 | F | 300 | " | Dyspnea and stridor at intervals | 24 hrs. | As in (2 and 3) |
| Guinea pig 6 | M | 280 | " | Respiration labored for several hours prior to death | 4 days | Several hours elapsed between death and postmortem examination. Postmortem changes advanced |
| Guinea pig 7 | F | 350 | " | Uneventful | 24 hrs., sacrificed | Lungs and respiratory passages: Essentially negative |
| Guinea pig 8 | F | 400 | " | " | 36 hrs., sacrificed | " " |
| Guinea pig 9 | M | 300 | " | " | 48 hrs., sacrificed | " " |

TABLE III—*Concluded*

| No. | Sex | Weight | Anesthesia | Clinical course | Survival | Pathology |
|---|---|---|---|---|---|---|
| | | *gm.* | | | | |
| Rabbit 1 | M | 1200 | Nembutal | Dyspnea and stridor at intervals throughout course | 22 hrs. | Lungs: Areas of marked congestion and pneumonic consolidation<br>Respiratory passages: Small amount of viscid mucus in larynx and trachea |
| Rabbit 2 | F | 1000 | " | " " | 28 hrs. | " " |
| Rabbit 3 | M | 1500 | " | Dyspnea and stridor on exertion. Respiration labored for several hours prior to death | 10 days | Lungs: Extensive areas of pneumonic consolidation<br>Respiratory passages: Small amount of serous fluid |

denominator in all cases in which pulmonary congestion and edema were seen in any degree was respiratory obstruction. In all experiments, brief or prolonged, in which significant pulmonary change was absent, a free airway had been maintained. The failure to obtain much more than a 30 hour survival in the rat was directly attributable to the failure to avoid occlusion of the respiratory tract. Apparently because of a larger glottis, the guinea pig and rabbit were better able to tolerate immobilization of one vocal cord, as described.

The effects of vagotomy, however, are not negligible, since, as was seen, paralysis of the vocal cords can be tolerated for many days by animals that will die soon after vagotomy is added thereto. The precise manner in which obstruction and vagotomy each contributes to the findings described here and elsewhere (4, 6) is beyond the scope of this report. However, a number of suggestions may be entertained. Asphyxial respiratory efforts resulting from obstruction are probably of importance as they mechanically affect the pulmonary vascular bed through intrathoracic pressure change, tracheal stenosis by itself being capable of producing pulmonary congestion and edema (15–17). Wide excursions of chest walls and diaphragm leading to a greater burden on the heart by increasing muscular work and creating pressure relationships unfavorable for optimum cardiac function (18–20), suggest another channel through which respiratory obstruction may operate. In this connection it should be pointed out that in the present studies pulmonary changes, when observed, were always more extensive and more intense in the waking animal operated under local anesthesia, and that in these animals, when respiratory block occurred, the asphyxial respiratory efforts were always more labored than in the narcotized animal. Con-

cerning the rôle of anoxemia produced by obstruction, Gibbs (21), in experiments with an artificial heart, found the lungs extremely sensitive to curtailment of the oxygen supply, and noted the striking effect of oxygen in combating pulmonary edema that developed in these preparations. In the intact animal anoxemia must, in addition, embarrass the heart. In Farber's (6) experiments on the guinea pig the routine use of artificial respiration was instituted to avoid asphyxial effects. However, our experience would indicate that gentle suction applied to the mouth of the tracheal cannula, as described by this author, was not sufficient to maintain a free air-way. As noted previously, the valve-like action of even small amounts of viscid secretion may produce a notable obstruction, the mechanism being missed at postmortem. Concerning the contribution of bilateral vagotomy to the changes under consideration, in an animal with lungs rendered hyperemic by denervation, degrees of respiratory obstruction readily tolerated by the intact animal may greatly affect total ventilation, since as Drinker, Peabody, and Blumgart (22) have shown, pulmonary engorgement produces a significant decrease in vital capacity. In addition, in the animal breathing spontaneously, the absence of the afferent respiratory pathway may contribute further to a disparity between respiratory needs and ventilation, during a period of embarrassment. Further, the decreased elasticity of the hyperemic lung (22) raises the question of what rôle artificial respiration itself might have played in Farber's (6) results. A too vigorous use of artificial respiration alone may cause pulmonary congestion and edema. Possibly a degree of inflation found satisfactory in the normal might prove excessive in the denervated lung, were this factor carefully controlled. As stated at the outset, a hyperemia alone may not be expected to produce lung edema in the presence of a vigorous circulation (and in the absence of respiratory obstruction), unless a permeability change is assumed (4). Such an assumption seems unwarranted by the findings of this study. In this connection it is of interest to note that Drinker, Peabody, and Blumgart (22), in producing decreased ventilation in the intact cat by compression of the pulmonary veins, found that in a certain number of experiments changes in ventilation were irreversible. Examination of the lungs revealed congestion and edema. The blood pressures in these animals had fallen steadily throughout the experiment, indicating that circulatory failure had contributed to stagnation of blood in the lungs. This is a not uncommon laboratory experience. The predominantly dependent distribution of congestion and edema noted in the present study suggests that a failing circulation played a rôle in producing these changes.

Merely observing regular heart action through an open chest (6) cannot be accepted as conclusive evidence that the heart is an unimportant factor. It seems likely that the burden thrown upon the cardiovascular system by obstructive asphyxia will be met less efficiently in the absence of a cardiovascular and respiratory regulator as important as the vagus.

## SUMMARY

1. Small animals (rat and guinea pig) vagotomized in the neck die within a period of hours, the lungs showing extensive congestion and edema.

2. Tracheotomy permits appreciably longer survival with minimal lung changes approximating those seen in the control animals.

3. Intrathoracic vagotomy (sparing the recurrent laryngeal nerve) on one side, and cervical vagotomy on the other, permits almost indefinite survival (guinea pig and rabbit), unless laryngeal paralysis from the unilateral denervation produces respiratory obstruction (rat, guinea pig, and rabbit).

4. Pulmonary edema following bilateral vagotomy probably results primarily from respiratory obstruction. It is suggested that circulatory failure may also be a factor of some importance. The rôle of vagotomy itself is considered in relationship to these two phenomena.

5. The reaction of smaller animals to bilateral vagotomy, with regard to lung changes, apparently differs in no way from that of the larger animals, but is less readily demonstrated because of the smaller diameters of the air passages.

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