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Studies on Postoperative Pulmonary Complications after  
Surgery for Esophageal Cancer : Especially the  
Relationship between the Vagus Nerve  
and the Pulmonary Complication  
Part 2 : Experimental Investigation

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**Introduction**

Most of the patients with esophageal cancer are old; they are in a condition of malnutrition and often with complications such as cardiopulmonary diseases.

As described in the previous publication<sup>28)</sup>, the review of the operated cases of esophageal cancer in our clinic showed that pulmonary complications represented the most frequent postoperative complications, resulting in "operative death" in many cases.

These postoperative pulmonary complications frequently occurred in patients operated for cancer involving the upper two-thirds of the thoracic esophagus. In the majority of cases the main lesions were located in the anterior wall of the esophagus near the bifurcation of the trachea and they definitely invaded the adventitia or the neighboring structures.

These facts suggest that injury of branches of the vagal nerve and of the posterior pulmonary plexus and interruption of the pulmonary lymph flow play important roles in the occurrence of the postoperative pulmonary complications.

Thus, the author made the following experiments in an attempt to elucidate the pulmonary pathophysiology after vagotomy.

**Materials and Methods**

1) Preparation of animals

Guinea pigs were selected for this study, because it is difficult to cause manifest pulmonary changes by vagotomy alone in dogs or rabbits<sup>7)18)39)</sup> while it is possible to do so in guinea pigs<sup>8)18)</sup> or rats<sup>17)18)32)</sup>.

The guinea pigs used, mongrel and of both sexes, varied in weight from 300 to 550 gm. Anesthesia such as with ether<sup>12)</sup> was not used in consideration of its possible effects

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Key words : Esophageal Cancer, Pulmonary Edema, Vagotomy, Pulmonary Hemodynamics, Hypoxia  
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on the lung. The guinea pigs were fixed on the table in the supine position. Through a mid-line incision in the neck, both vagi were isolated and held by loose ligatures. They were killed by intracardiac injection of pentobarbital sodium immediately after thoracotomy. This method was used so that breathing exercises and cardiac functions would stop at the same time, because if breathing stops before cardiac arrest, pulmonary congestion or exudation of fluid may develop due to inflow of blood into the lung in a condition of hypoxia

2) Gross findings of the lung and measurement of the water content of the lung

The water contents of the lungs of the guinea pigs which were sacrificed 30, 60, 90, 120, 150 and 180 minutes after bilateral cervical vagotomy, were measured according to EATON'S<sup>6)</sup> method. Removed lungs were dropped into previously weighed glass-stoppered bottles. The bottles containing wet lungs were weighed, the stoppers were then removed, then bottles and stoppers were placed in a drying oven for seventy-two hours at 60°C, then two more hours at 100°C. At the end of the seventy-four hour drying process, the bottles were reweighed and the per cent of moisture in the lungs was computed.

3) Arterial blood gas analysis after bilateral cervical vagotomy

A cannula (Tube for use in epidural anesthesia) was introduced into the carotid artery before bilateral cervical vagotomy. Arterial blood was drawn into the capillary tube every 30 minutes after vagotomy. PaO<sub>2</sub>, PaCO<sub>2</sub>, PH, HCO<sub>3</sub><sup>-</sup>, total CO<sub>2</sub> and base excess were measured with a blood gas analyzer (Corning, Model 160).

4) Microscopic findings of the lung after bilateral cervical vagotomy

Both lungs were removed every 30 minutes after bilateral cervical vagotomy. The lungs were immersed in 10 per cent formalin and then were stained with hematoxyline-eosin.

5) Investigation of changes in vascular permeability of the lung after bilateral cervical vagotomy.

i) A fluorohistological study using the FITC dextran method<sup>26)</sup>

Ten w/v% FITC dextran (fluorescein isothiacyanate dextran, molecular weight approximately 39,000), 1 ml per 100mg of body weight, were injected into the external jugular vein after bilateral cervical vagotomy. Fifteen minutes later, the lungs were removed rapidly and immediately frozen in isopentan cooled by dry ice acetone and then freeze-dried for 5 days. These specimens were embedded in paraffin and cut into sections each approximately 10 $\mu$  thick.

An Olympus FLM fluorescence microscope with filters was used for the observations (excitation filter: B2, barrier filter: Y52).

ii) Determination of dextran in the lung

Low molecular dextran, 1 ml per 100 mg of body weight, was injected into the external jugular vein after bilateral cervical vagotomy. Fifteen minutes later, the lungs were removed. The quantity of dextran in the lung was measured by the anthrone method<sup>33)38)</sup> using the Hitachi spectrophotometer (139 UV-VIS spectrophotometer).

6) The experiment of stimulation on the vagal nerves

i) The cervical vagal nerve on one side was severed and both (peripheral or central)

stumps were stimulated electrically.

ii) The cervical vagal nerve on one side was severed and that on the other was stimulated electrically using AN-EL instrument electrostimulator with a bipolar electrodes. The vagal nerves were stimulated for 60 seconds under a condition adjusted from 0.1 mV to 5 mV in power, from 10 HZ to 30 HZ in frequency, and at 1 m sec intervals.

The animals were killed at 90 minutes after stimulation, because the water contents of the lungs significantly increased from 90 minutes after bilateral cervical vagotomy. And the lungs were observed and the water content of the lung was measured.

#### 7) Experiment on the cervical sympathectomy

i) Bilateral cervical sympathectomy alone or bilateral vagotomy 30 minutes after bilateral sympathectomy were done, and water content of the lung was measured.

ii) Unilateral or bilateral sympathectomy and bilateral vagotomy were done at the same time. The sympathectomy was performed at two positions, one cranial and the other caudal to the brachial plexus. The animals were killed 90 minutes after the section, and water contents of the lungs were measured.

### Result

Immediately after cutting the bilateral cervical vagi the respirations became slow and deep. The forced inspiration gradually appeared. Foam poured out of the nose and the mouth after about 90 minutes.

The guinea pigs died three or four hours after bilateral cervical vagotomy. When the

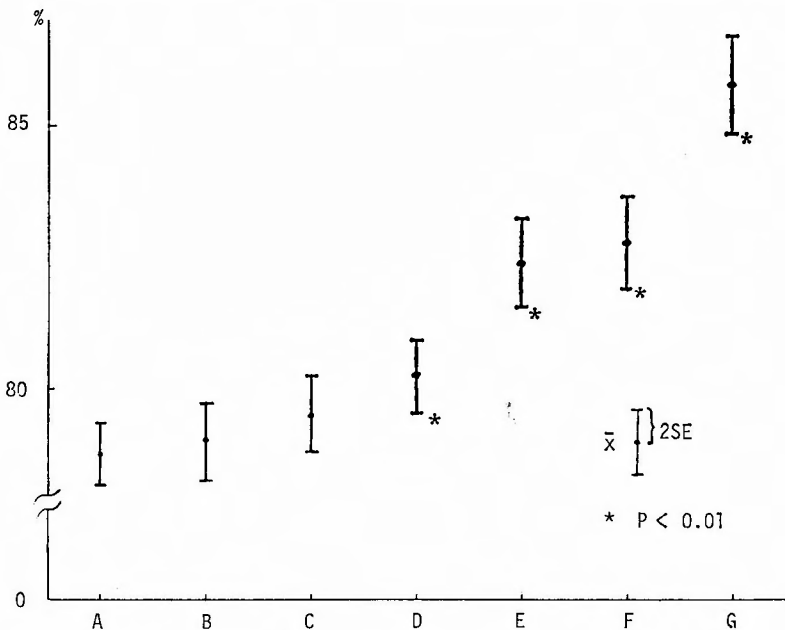


Fig. 1 The water content of the lung began increasing from about 90 minutes after bilateral cervical vagotomy.

**Table 1.** Water Content of the Lung following Bilateral Cervical Vagotomy  
One-way Analysis of Variance Table

SV	SS	DF	V	F <sub>o</sub>	P
Main Effect	205.4166	6	34.2361	38.6924	<0.01
Error	33.6234	38	0.8848		
Total	239.0400	44			

SV: Source of Variation    SS: Sums of Squares    DF: Degree of freedom    V: Variances  
F<sub>o</sub>: Variance ratio        P: Probability

Mean Table

	A	B	C	D	E	F	G
n	10	7	7	8	4	5	4
$\bar{x}$	78.78	79.01	79.50	80.26	82.40	82.80	85.80
SE	0.297	0.356	0.356	0.333	0.470	0.447	0.470

n: Sample Size     $\bar{x}$ : Mean Value    SE: Standard Error

p Matrix due to Student's t

B	—					
C	—	—				
D	**	*	—			
E	**	**	**	**		
F	**	**	**	**	—	
G	**	**	**	**	**	**
	A	B	C	D	E	F

A: Guinea pigs, with no vagotomy (controls)  
B:                   , Sacrificed 30 minutes after vagotomy  
C:                   ,                   60  
D:                   ,                   90  
E:                   ,                   120  
F:                   ,                   150  
G:                   ,                   180

— NS  
\* P < 0.05  
\*\* p < 0.01

tube was inserted in advance into the trachea by tracheotomy, the forced inspiration was very mild. But about 120 minutes later, foam poured out and the animals eventually died four or five hours after bilateral cervical vagotomy.

1) The gross findings of the lung and measurement of the water content of the lung  
The water content of the lung began increasing about 90 minutes after bilateral cervical vagotomy and 180 minutes later it increased remarkably. The value of the water content of the lung which was removed rapidly after death was  $85.8 \pm 0.47\%$  (mean  $\pm$  ISE), significantly higher than the value of the control group ( $78.78 \pm 0.297\%$ ) (Table 1, Fig. 1). The lungs of guinea pigs show a characteristic gross appearance: the left lung is

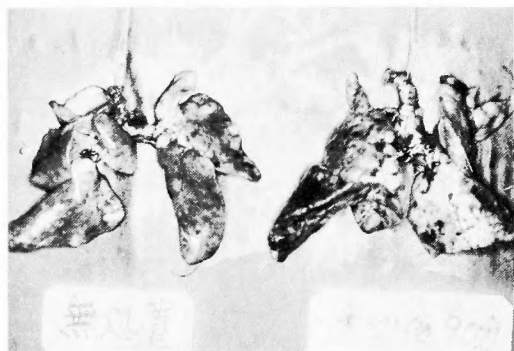


Fig. 2. Left side: The specimen of the lung with no vagotomy (Control).  
 Right side: The specimen of the lung 90 minutes after bilateral cervical vagotomy.  
 The lung became increasingly congested and hemorrhagic remarkably.

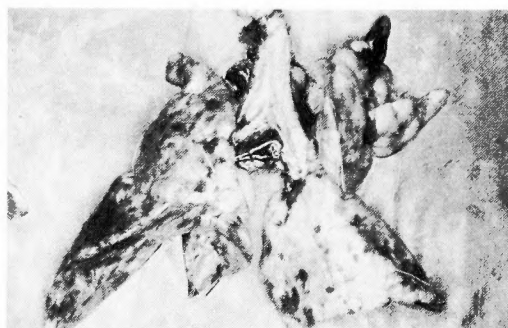


Fig. 3. The specimen of the lung 90 minutes after bilateral cervical vagotomy.  
 The foams were recognized in the trachea.

Table 2. Arterial Blood Gas Analysis after Bilateral Cervical Vagotomy (PaO<sub>2</sub> and PaCO<sub>2</sub>)

One-way Analysis of Variance Table

	SV	SS	DF	V	Fo	P
O <sub>2</sub>	Main Effect	9096.6402	6	1516.1067	17.4873	<0.05
	Error	2167.4385	25	86.6975		
	Total	11264.0787	31			
CO <sub>2</sub>	Main Effect	600.1405	6	100.0236	1.5858	NS
	Error	12789.5260	25	511.5810		
	Total	21054.8047	31			

Mean Table

	PO <sub>2</sub>			PCO <sub>2</sub>		
	n	$\bar{x}$	SE	n	$\bar{x}$	SE
Control	6	86.28	4.3934	6	38.87	3.4263
30'	5	44.28	4.0062	5	45.94	2.2173
60'	4	52.93	5.6417	4	46.38	1.5624
90'	5	51.48	5.5440	5	48.34	3.7681
120'	4	40.60	2.9306	4	50.58	6.0758
150'	5	40.90	2.6554	5	51.18	4.0256
180'	3	37.93	2.1074	3	51.03	3.1798

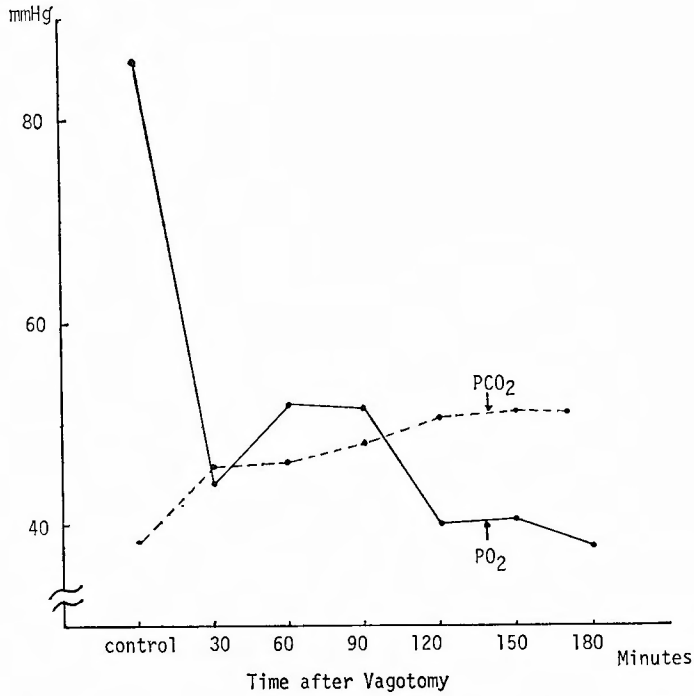


Fig. 4. PaO<sub>2</sub> immediately dropped after vagotomy and reached the minimum at about 30 minutes. PaCO<sub>2</sub>, on the other hand, showed a tendency to rise after vagotomy, but the elevation was not statistically significant.

Table 3 Blood Gas Analysis after Vagotomy (HCO<sub>3</sub><sup>-</sup>, TCO<sub>2</sub>, B.E, PH)  
One-way Analysis of Variance Table

	SV	SS	DF	V	F <sub>0</sub>	P
HCO <sub>3</sub>	Mean Effect	8265.2787	6	1377.5463	2.6927	<0.05
	Error	1576.9070	25	63.0763		
	Total	2177.0475	31			
TCO <sub>2</sub>	Mean Effect	8046.2122	6	1341.0345	2.5969	<0.05
	Error	12909.9951	25	516.3998		
	Total	20956.2073	31			
B.E.	Mean Effect	6301.7705	6	1050.2950	2.5879	<0.05
	Error	10146.1495	25	405.8460		
	Total	16447.9200	31			
PH	Mean Effect	0.2282	6	0.0380	1.5261	NS
	Error	0.6215	25	0.0249		
	Total	0.8497	31			

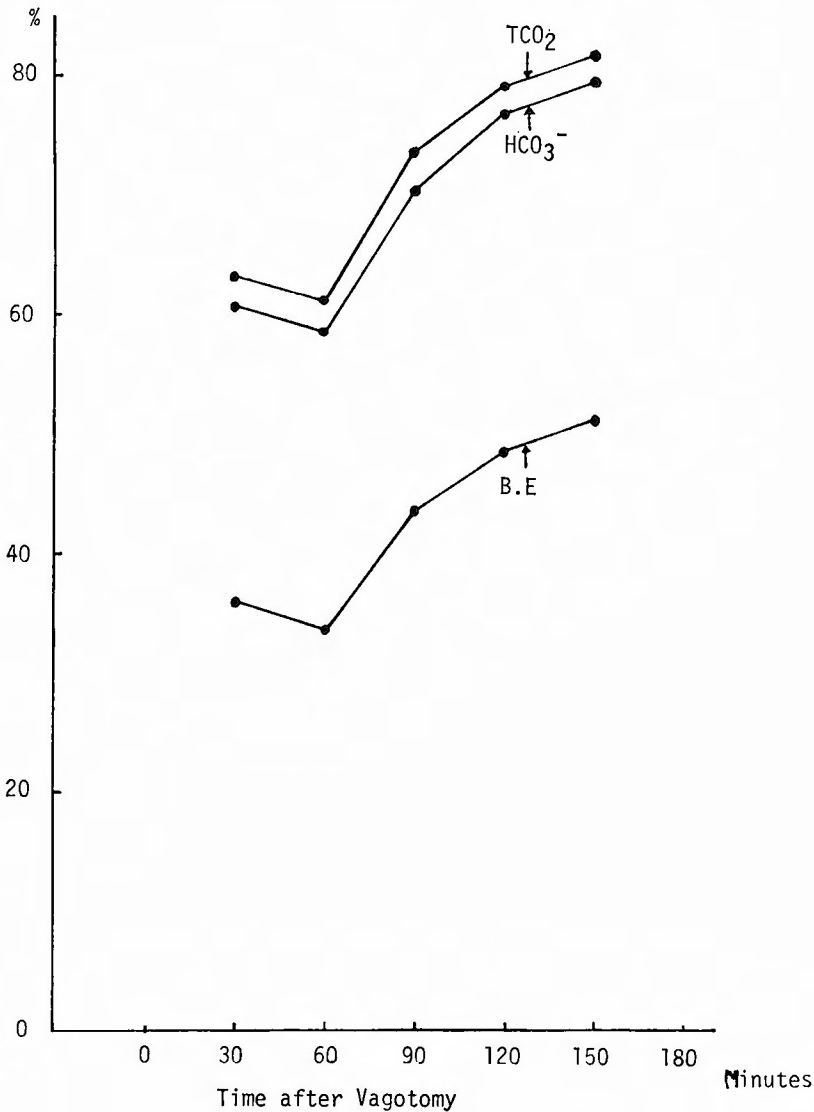


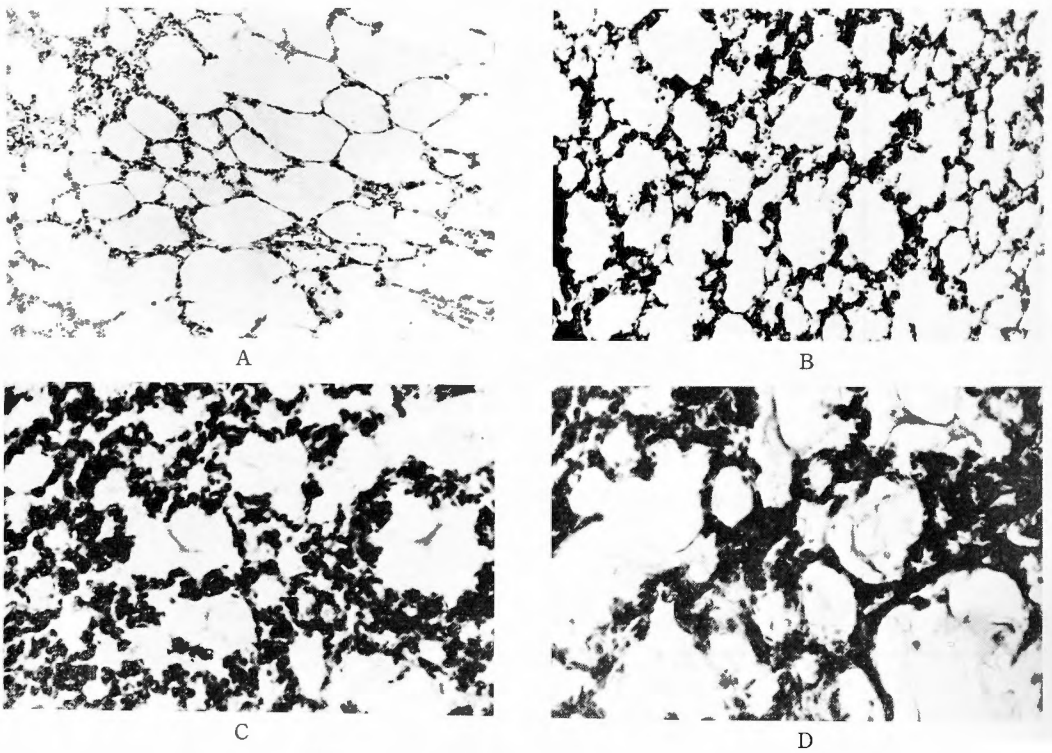
Fig. 5. HCO<sub>3</sub>, total CO<sub>2</sub> and base excess were treated these values by moving average method. They showed a similar pattern.

separated into three lobes and the right lung is separated into four lobes of various size. After vagotomy, as time went on, the lungs became increasingly congested and from about 90 minutes onward they became remarkably hemorrhagic. The lungs were deep red and edematous, resembling the liver (Fig. 2). Meanwhile, the foam in the trachea increased as time went on (Fig. 3). In our experiment throughout the year, the water contents of the lungs in summer were different from these in winter. Changes in the water contents of the lungs were not remarkable in winter. Some guinea pigs survived more than 12 hours in winter.



## 2) Arterial blood gas analysis after bilateral cervical vagotomy

In the measurement at 30 minutes after vagotomy, the value of the arterial  $O_2$  tension ( $PaO_2$ ) was  $44.28 \pm 4.01$  mmHg, remarkably lower than the prevagotomy value of  $86.26 \pm 4.39$  mmHg. Then it slightly rose but it gradually dropped again as time went on.  $PaO_2$ , when measured at 10 minutes after vagotomy, had already become 50.0 mmHg.  $PaO_2$  immediately dropped after vagotomy and reached the minimum at about 30 minutes (Table 2, Fig.4).  $PaCO_2$ , on the other hand, showed a tendency to rise after vagotomy, but the elevation was not statistically significant. As for  $HCO_3^-$ , total  $CO_2$ , base excess and PH, the author treated these values by the moving average method. As shown in Table 3, they had a similar pattern (Table 3, Fig. 5).



- A No vagotomy (Control).  
The alveolar septum did not thicken and alveolar spaces were well preserved. ( $\times 40$ )
- B 30 minutes after bilateral cervical vagotomy.  
Alveolar spaces were relatively preserved, but inflammatory cells slightly infiltrated into the alveolar septa. ( $\times 40$ )
- C : 60 minutes after bilateral cervical vagotomy.  
Alveolar spaces became slightly dilated and a little acidophilic fluid were present in the slightly dilated alveolar spaces. ( $\times 100$ )
- D . 90 minutes after bilateral cervical vagotomy  
The inflammatory cells, such as neutrophils, lymphocytes and monocytes remarkably infiltrated into the enlarged alveolar septa. Furthermore, dilated capillaries and the extravasation of the red cells were noted in the alveolar walls. Acidophilic fluid was present remarkably in alveolar spaces. ( $\times 200$ )

Fig. 6. Photomicrographs show pathohistological findings of the lung. (hematoxyline and eosin)

### 3) Microscopic findings of the lung (Fig. 6 : A, B, C, D)

In the control group, the alveolar septum did not thicken and alveolar spaces were well preserved. From about 60 minutes after vagotomy, alveolar spaces became slightly dilated and acidophilic fluid was observed in the alveoli. A little acidophilic fluid was present in the slightly dilated alveolar spaces. The inflammatory cells, such as neutrophils, lymphocytes and monocytes were moderately infiltrated into the enlarged alveolar septa. Furthermore, dilated capillaries and a slight extravasation of the red cells were noted in the alveolar walls. There were some places which became atelectatic.

### 4) A fluorohistological study using FITC dextran method

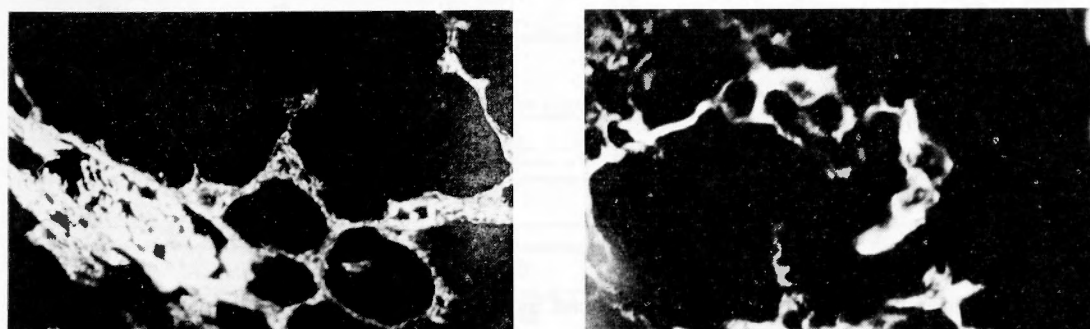
FITC dextran was found localized within the alveolar vessels in the control group. From about 60 minutes after vagotomy, FITC dextran infiltrated from the alveolar vessels into the interstitial. Later it was also found in the alveolar spaces (Fig. 7).

### 5) Determination of dextran using the anthrone method

The concentration of dextran in the lung did not show any statistically significant differences between the vagotomized group and the control group until 60 minutes after vagotomy. But it significantly increased from 90 minutes after vagotomy and remarkably increased 150 minutes later (Table 4). These facts suggested that the dextran exuded from the vessels and was gradually transferred into the alveolar septum or into alveolar spaces because of increased pulmonary permeability.

### 6) The experiment of stimulation on the vagal nerve

Any difference in the water content of the lung was not recognized between the unilaterally vagotomized group and the control group. The experiment on the group, vagotomy on one side and electrical stimulation on the other, was performed by the experimental design (three factors design), and the factors and the levels are indicated in Table



A

B

A : No vagotomy (Control).

The intense yellow fluorescing FITC dextran was confined to the alveolar vessels. ( $\times 100$ )

B : 60 minutes after bilateral cervical vagotomy

The intense yellow fluorescing FITC dextran infiltrated from the alveolar vessels into the interstitial. ( $\times 100$ )

Fig. 7. Photomicrographs show fluorohistological findings of the lung using FITC dextran.

**Table 4.** Determination of Dextran in Lung with Anthrone following Bilateral Cervical Vagotomy

Minutes	Mean	SE
0	24.48	7.746
30	21.75	13.417
60	29.10	9.487
90	69.56	8.486
120	75.03	9.487
150	118.95	9.487

$Du/DS \times 0.1 \times$  dilution of plasma  $\times 100 \times 0.9$   
=mg. of dextran per 100ml.

Du: The optical density of the unknown  
DS: The optical density of the standard

p Matrix due to Student's t

30	—				
60	—	—			
90	**	—	*		
120	**	*	**	—	
150	**	*	**	*	*
	0	30	60	90	120

— NS  
\*  $p < 0.05$   
\*\*  $p < 0.01$

**Table 5.** Water Content of the Lung for Electrical Stimulation of Vagal Nerve due to Experimental Design.

Factor and Level (Three Factors Design)

Factor	Level			
A Method of Operation	A <sub>1</sub> : R, Electrical stimulation L, Vagotomy		A <sub>2</sub> : R, Vagotomy L, Electrical Stimulation	
B Frequency	B <sub>1</sub> : 10 HZ		B <sub>2</sub> : 30 HZ	
C : Power	C <sub>1</sub> : 0.1 mV	C <sub>2</sub> : 0.5 mV	C <sub>3</sub> : 1.0 mV	C <sub>4</sub> : 5.0 mV

Analysis of Variance Table

SV	SS	DF	V	Fo	P
A	1.0512	1	1.0512	—	—
B	0.32	1	0.32	—	—
C	30.6175	3	10.2058	8.9927	<0.10
Error	29.5063	26	1.1348		
Total	61.495	31			

5. The water content of the lung increased as the power became stronger, but it showed a converse tendency to decrease when power was more than 0.5 mV. Any difference between both right and left sides for electrical stimulation was not recognized. Also in the group of vagotomy on one side and electrical stimulation on its both stumps, there was no significant difference as compared with the control group (Table 5, Fig. 8).

7) The experiments on the sympathectomy

There were no significant changes in the water content of the lung of the group of bilateral cervical sympathectomy.

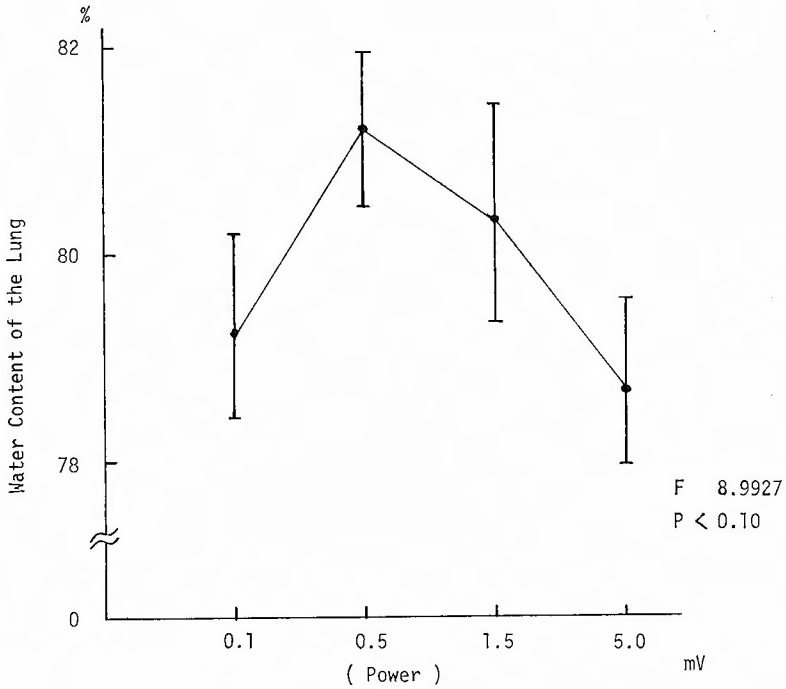


Fig. 8. The water content of the lung increased as the power became stronger, but it showed a converse tendency to decrease when power was more than 0.5mV.

Table 6 Comparison of Experiments on Sympathectomy and Other Experiments  
One-way Analysis of Variance Table

SV	SS	DF	V	Fo	P
Main Effect	52.5494	3	17.5165	18.9757	<0.01
Error	29.5381	32	0.9231		
Total	82.0875	35			

Mean Table

	A	B	C	D
n	10	8	6	12
$\bar{x}$	78.78	80.26	80.83	81.85
SE	0.304	0.340	0.392	0.277

- A : No Vagotomy (Controls)
- B : 90 Minutes after Bilateral Vagotomy
- C : Bilateral Vagotomy and Sympathectomy at the same time
- D : Bilateral Vagotomy 30 Minutes after Bilateral Sympathectomy

p Matrix due to Student's t

B	**		
C	**	—	
D	**	**	*
	A	B	C

— NS  
\* p<0.05  
\*\* p<0.01

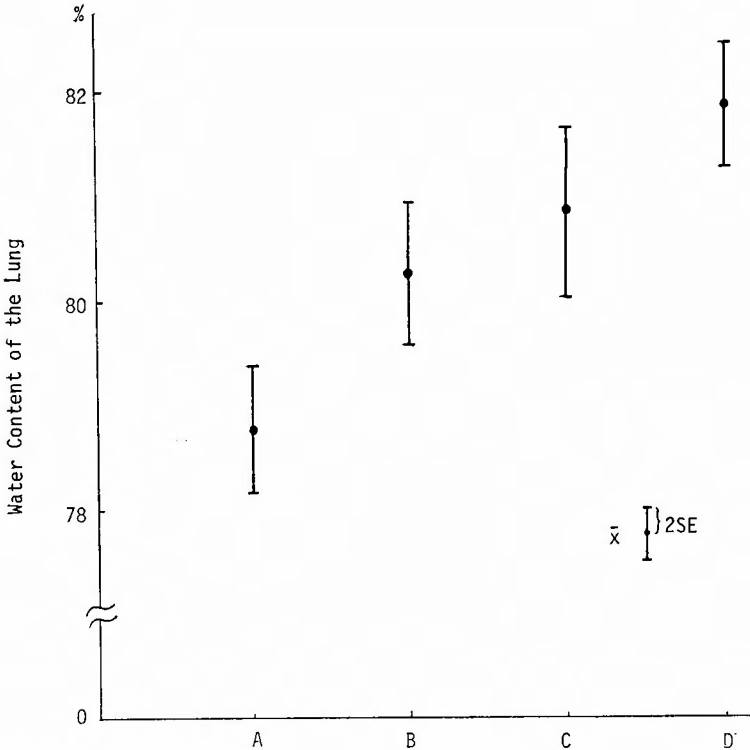


Fig. 9. In the group in which bilateral sympathectomy was done at 30 minutes before vagotomy, the water content of the lung had significantly increased as compared with any other groups.

In the group in which bilateral sympathectomy was done at the same time as bilateral vagotomy, there was no difference in the water content of the lung as compared with the vagotomized group.

In the group in which bilateral sympathectomy was performed at 30 minutes before vagotomy, the water content of the lung had significantly increased as compared with any other groups (Table 6, Fig. 9).

### Discussion

The causative factors of postoperative pulmonary complications of esophageal cancer can be summarized as follows:

1) Most of the patients with esophageal cancer are relatively old, consequently many of them are in a condition of hypoproteinemia and malnutrition, or have complications such as pulmonary emphysema, pulmonary fibrosis, chronic bronchopneumonia and hypofunction in the cardiopulmonary system.

2) Increase in bronchial secretion is caused by intratracheal intubation, stimulation to the mucous membrane of the air passage by inhaled gas and trauma of the trachea.

3) The operation takes a long time during which one lung or occasionally both lungs are in a condition of collapse.

4) The higher the resected portion of the esophagus is, the more the vagal nerves are injured. Bilateral vagal trunks may be severed when the resected portion is below pulmonary hilus.

5) The cleansing of the mediastinal and epibronchial lymph nodes during the operation for esophageal cancer inevitably causes interruption of pulmonary lymph flow.

6) In the case of intrathoracic reconstruction, dilatation of the elevated gastric tube and pneumothorax affect the cardiopulmonary function.

In the case of antethoracic reconstruction, postoperative aspiration pneumonia frequently occurs.

7) The chest movement is markedly restricted by postoperative pains; as a result, expulsion of sputum becomes insufficient.

8) Large quantities of fluid and blood transfusion during the operation and postoperative period are etiologically concerned with severe pulmonary edema.

Among these factors, nervous factor (injury of the vagal nerves), interruption of pulmonary lymph flow by the cleansing of the mediastinal and epibronchial lymph nodes, hypoproteinemia, and malnutrition seem to be closely related with pulmonary complications after operation for cancer of the upper two-thirds of the thoracic esophagus.

As STAUB<sup>41)</sup> described, when lung tissue sustains trauma by oppression during the operation on the thorax, pulmonary fluid easily transudes into the interstitial space due to elevated pulmonary capillary pressure.

Even a slight increase in total pulmonary fluid volume causes abnormal X-ray finding and decreases arterial O<sub>2</sub> tension (PaO<sub>2</sub>) beyond expectation.

The innervation of the vagus nerves to the thoracic esophagus, especially around the bifurcation of the trachea, is as follows<sup>42)</sup>: Both vagus nerves are intimately associated anatomically and functionally with the esophagus. The general gross arrangement may be simplified for the moment by stating that the vagi emerge from their pulmonary plexus behind the right and left lung roots, respectively, divide into several branches, and become arranged along the anterior and posterior surfaces and become as the complicated nets of the esophageal plexus.

Behind the bifurcation of the trachea each of the vagus nerves is subdivided into two or three bundles held together by a fascial sheath and communicates with the corresponding nerve on the opposite side by anastomotic transverse branches which make up the pulmonary plexus. This plexus anastomoses in turn with the thoracic sympathetic chain, which participated in the innervation of the esophagus at this point by way of the aortic plexus which is in turn made up of filaments from the second to the seventh thoracic ganglia (Fig. 10).

NADEL<sup>29)</sup> described that the pulmonary plexus consists of branches of vagal nerves and thoracic sympathetic trunks.

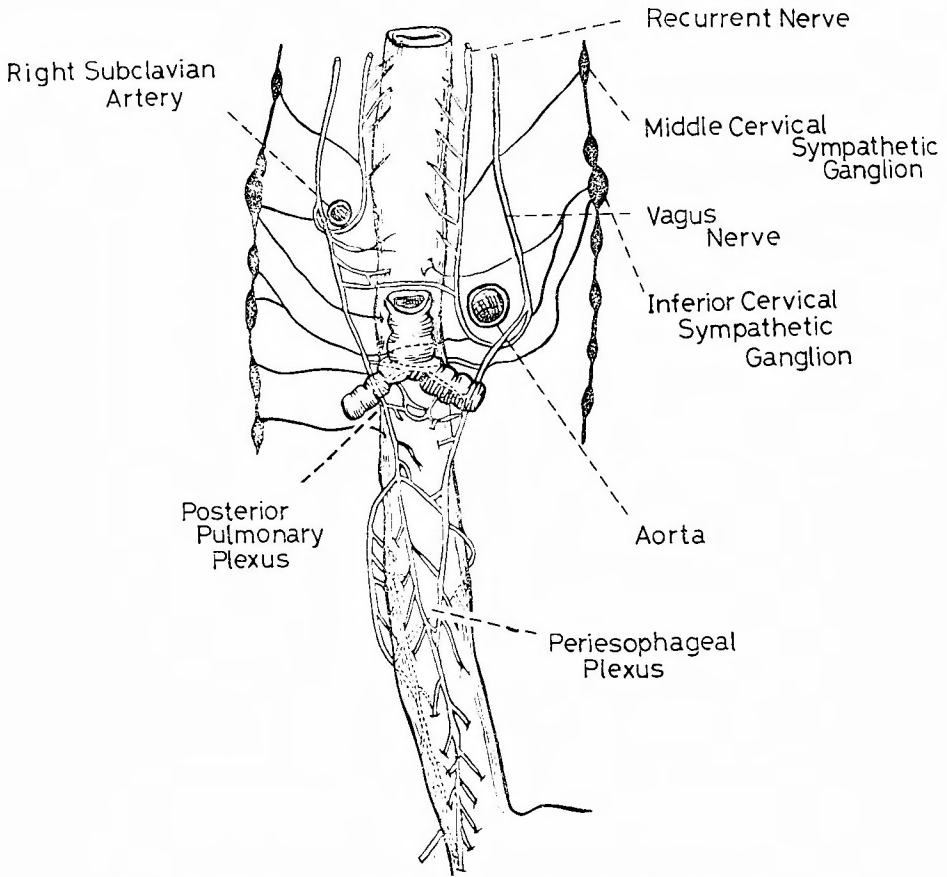


Fig. 10 Innervation of the esophagus by the vagus nerves.

And these terminals are subdivided into bronchial smooth muscles, blood vessels, bronchial glands and mucous epithelia. Bronchoconstrictor fibers separate from the vagal nerve, while bronchodilator fibers separate from the sympathetic nerve.

Subepithelial receptors (cough receptors), which are afferent terminal vagal nerves, are the starting point of the ascending way and many of them are present at the bifurcation of the trachea. These are probably concerned with reflexive constriction of the airway.

These anatomical findings indicate that when resection of the main lesion located in the anterior wall of the esophagus near the bifurcation and the cleansing of lymphnodes are performed during the operation for cancer of the upper two-thirds of the thoracic esophagus, branches of the vagal nerve and the posterior pulmonary plexus tend to be injured and postoperative pulmonary complications may occur<sup>28)</sup>.

Since FREY in 1887 reported on the relationship between vagal nerve and pulmonary complications, pulmonary edema especially has been the subject of a great deal of experimental studies.

FARBER<sup>7)8)9)</sup> (1937) found heavy pulmonary edema in rabbits and guinea pigs after vagotomy with and without tracheostomy. He also reported that neuropathic pulmonary edema in the guinea pig was caused by disturbance or abolition of the pulmonary vasomotor nerves. And he suggested that neuropathic pulmonary edema in man was caused by disturbance, either central or peripheral, of the vasomotor control of the pulmonary vessels. Laryngeal paralysis (aspiration of food, slow asphyxia) was not an essential factor in the production of severe pulmonary edema and death following bilateral cervical vagotomy.

LORBER<sup>18)</sup> and REICHMAN<sup>32)</sup> concluded that the important factor in pulmonary edema following bilateral vagotomy was inspiratory obstruction. In an experiment by KIMURA and the author, tracheotomy was performed to prevent the effect of laryngeal obstruction before bilateral cervical vagotomy in the guinea pig, but animals died of pulmonary edema within 5 or 6 hours. Thus the author can not agree with LORBER's opinion.

SCHMITT<sup>37)</sup> described on the basis of his experimental studies that cervical vagal section was rapidly fatal to the guinea pig and the process was one of pulmonary hyperemia followed usually but not necessarily by transudation. He also reported that factors incidental to laryngeal paralysis or to tracheostomy were not implicated in the production of pulmonary edema.

HARRISON and LIEBOW<sup>10)</sup> reported that pulmonary edema developed in dogs after vagotomy only when saline solution of 100 ml or more per kilogram per minute was administered.

WAKIZAKA<sup>46)47)</sup> also reported that when pulmonary lobectomy or transfusion was additionally performed in vagotomized dogs, severe pulmonary edema frequently occurred. These experiments suggest that injury of the vagal nerve during the operation for cancer of the thoracic esophagus may cause pulmonary edema by postoperative overtransfusion.

TOMITA<sup>44)</sup> et al. indicated a few years ago that, during the operation for cancer of the thoracic esophagus, the vagal nerve branches to the pulmonary artery and bronchus were resected because of extensive resection of the mediastinal lymph nodes, which resulted in the unbalance of the pulmonary circuits and change in the alveolar capillary permeability.

INOKUCHI<sup>13)</sup> resected extensively the thoracic vagal nerves and branches to the lungs using animals and observed microatelectasis in the lungs 2 or 3 days after the operation. He indicated that this was caused by decrease in bronchial ciliary movement and cough reflex because of denervation, defective expulsion of bronchial secretion, and decrease in ventilatory volume. In the author's experiments using guinea pigs, a gradual increase in the water content of the lung by EATON<sup>6)</sup>'s method was shown to have developed 90 minutes after vagotomy. (In KIMURA<sup>16)</sup>'s experiments, its increase appeared from 45 minutes onward).

The water content of the lung in the control group was about 78% as compared with 74-75% in KIMURA<sup>16)</sup>'s experiment.

In the experiments throughout the year, the water content of the lung after cervical vagotomy increased in summer more easily than in winter. Some animals survived more than twelve hours in winter.

MATSUO<sup>25)</sup> made the following assumption as to the experiments of cervical sympathe-



ctomy: sympathicotonic state being different between in summer and in winter, the effect of sympathectomy remarkably appears in winter because of sympathicotonic state but not in summer because of the absence of sympathicotonic state.

The author thinks the reverse state of this may appear in vagotomy.

In the author's experiments, no difference in the water content of the lung was observed between the control group and the group of unilateral cervical vagotomy.

But in the group in which the vagal nerve was severed on one side and stimulated electrically on the other, the water content of the lung increased as the power became strong, reaching the peak at 0.5 mV and then decreasing.

NISHII<sup>45)</sup> maintained that weak electric stimulation of the vagal nerve caused pulmonary vasodilatation, while strong electric stimulation of it caused pulmonary vasoconstriction.

TSUZI<sup>45)</sup> described that sympathetic stimulation constricted pulmonary vessels, while vagal nerve stimulation induced pulmonary vasodilatation and that such control of the pulmonary vessels by the vagal nerve, much weaker than that by the sympathetic nerve, was not effective enough.

Since GATES in 1917 and GLASS in 1928 described that pulmonary edema was caused by massive intravenous injection of adrenalin, there has been a great deal of experimental investigations on the problem with regard to the sympathetic nerve and pulmonary edema.

LUISADA<sup>19)20)21)22)</sup> reported that vagotomy tend to aggravate pulmonary edema caused by adrenalin, but unilateral sympathectomy and unilateral or bilateral stellate ganglionectomy conferred protective effects.

In the author's experiment, no statistically significant differences were recognized between the control group and the group of bilateral cervical sympathectomy or the group of bilateral cervical vagotomy in addition to bilateral cervical sympathectomy.

KIMURA<sup>16)</sup> reported that pulmonary edema was induced by bilateral cervical sympathectomy alone.

SARNOFF<sup>34)35)</sup> described that the so-called neurogenic pulmonary edema (NPE) was caused by inducing marked change on the cardiopulmonary hemodynamics through the sympathetic system. Therefore, he criticized the term "neurogenic pulmonary edema" and believed that a more adequate term is "neurohemodynamic pulmonary edema".

Since MOUTIR in 1918, it has been well known that pulmonary edema and respiratory failure are caused by brain trauma and elevated intracranial pressure accompanied by brain injury, thus designated as "neurogenic pulmonary edema".

MALIK<sup>24)</sup> described that the role of the sympathetic nervous system in pulmonary edema caused by increased intracranial pressure was the stimulation to the  $\alpha$ -fibers of the sympathetic nerve followed by cerebral ischemia and the cerebral vasoconstriction accompanied by that stimulation.

In any case, the involvement of the sympathetic nervous system in the vasomotor system seems to be the major factor in pulmonary edema.

KIMURA<sup>16)</sup> described that the pulmonary edema was caused by bilateral cervical vagotomy

30 minutes after bilateral cervical sympathectomy or bilateral cervical vagotomy alone.

This fact proves that the vagal nerves are concerned with pulmonary vasomotor system. The following mechanism based on the changes in pulmonary hemodynamics was suspected from our experiments.

In the group of bilateral cervical vagotomy or the group in which the vagus nerve was resected on one side and the nerve was stimulated electrically on the other (a strong stimulation beyond a certain extent constricts vessels), the same effects as that produced by stimulation of the sympathetic nerve took place.

As a result, the pulmonary vein and the pulmonary capillaries, especially the former, were constricted to elevate pulmonary capillaries pressure, then to cause pulmonary edema.

Bilateral cervical vagotomy 30 minutes after bilateral cervical sympathectomy produced the same effect as that produced by stimulation of vagal nerve, dilating the pulmonary vein and the pulmonary capillaries, especially the latter, to cause pulmonary edema.

There have been reported from EATON<sup>6)</sup>, JORDAN<sup>14)</sup>, WAKIZAKA<sup>46)47)</sup> et al. as to pulmonary edema classified into postoperative complications.

Among the factors which are thought to be the cause of pulmonary edema there are change in permeability of the pulmonary capillaries, left ventricular failure and neurogenic factors<sup>11)22)</sup>.

Moreover, regarding these etiological factors resulting in the unbalance between serum production and its absorption in alveoli, the following factors are involved as the factor to produce the serum, rise in the pulmonary capillary pressure, decrease in the alveolar pressure and anoxia, and as the serum absorptive factor, the lymphatic system in lung tissue.

JORDAN<sup>14)</sup> summarized the methods of producing pulmonary edema in experimental animals (Table 7).

**Table 7.** Methods of production of pulmonary edema in experimental animals. (Jordan)

- 
1. Heart-lung preparations
  2. Experiment causing an alteration in cardiac function
    - A. Increased resistance to blood flow
      1. Occlusion of the aorta
      2. Obstruction of the pulmonary veins
    - B. Ventricular damage
    - C. Administration of epinephrine
  3. Experiments causing alterations in pulmonary physiology
    - A. Pulmonary irritants
    - B. Respiratory resistance
      1. Inspiratory resistance
      2. Expiratory resistance
    - C. Trauma to thorax
  4. Neurogenic
    - A. Increased intracranial pressure
    - B. Stimulation of cardiovascular receptors
    - C. Vagotomy

ALTSCHULE described that the pulmonary vasomotor system was closely concerned with pulmonary edema and that the neurogenic factors considerably affected change in this system.

As previously described, even when tracheotomy was done before bilateral cervical vagotomy, the pulmonary edema occurred.

KIMURA<sup>16)</sup> reported that he made a stenosis at the trachea of the guinea pig artificially, but pulmonary edema did not occur.

He also investigated about airway obstruction or forced inspiratory effort, increase in permeability of the pulmonary capillaries and change in hemodynamics characterized by a specific pulmonary vasomotor system as the etiological factor of pulmonary edema following vagotomy. He stated that the forced inspiratory effort was a symptom of vagus nerve stimulation and as the cause of this phenomenon, he cited disappearance of Hering-Breuer reflex by vagotomy and change in lumen by constriction of smooth muscle because of the absence of cartilage in bronchiole.

SHULER<sup>40)</sup> reported that, since the right ventricular output increases and the left ventricular output decreases during inspiration, a great deal of blood is pooled in the pulmonary vascular bed during the forced inspiratory effort.

REICHSMAN<sup>32)</sup> explained that a markedly negative intra-alveolar pressure should be present during the forced inspiratory effort and this abnormal negative pressure would tend to overcome the osmotic pressure in the pulmonary capillaries and draw transudate into alveoli.

Recently SCHEAR<sup>36)</sup> reported some clinical cases of pulmonary edema caused by the negative intra-alveolar pressure.

The most interesting one among these cases was the patient with bleeding from the esophagus, in whom a Sengstaken-Blakemore tube was inserted but the flexed tube obstructed the larynx and moderate inspiratory obstruction caused pulmonary edema. He reasoned that the continuity of a markedly negative intra-alveolar pressure makes the transudate flow into the alveoli, and emphasized the danger which airway obstruction entails. The author measured the arterial  $O_2$  tension ( $PaO_2$ ) after bilateral cervical vagotomy. Thirty minutes later it had already decreased remarkably. There have been many experimental reports<sup>5)48)49)</sup> regarding the effect of hypoxia on the extravasation of fluid and plasma protein in the pulmonary system. Some investigators claimed that increase in transudation of pulmonary lymph flow causes pulmonary edema while others reported to the contrary, maintaining that hypoxia neither affects the permeability of pulmonary capillaries nor causes pulmonary edema.

DRINKER<sup>5)</sup> described that, in addition to increase in the pulmonary capillary permeability produced by neurogenic factor, one more factor, severe anoxia, was required in producing pulmonary edema.

BLAND<sup>4)</sup> et al. investigated the effects of hypoxia on lung lymph flow and protein transport in unanesthetized sheep breathing 10%  $O_2$ , and reported that hypoxia for 4 to 48

hours, alone or with increased pulmonary microvascular pressure, produced no change in lung fluid filtration or protein permeability. They argued that large increment in pulmonary lymph flow in response to sustained elevation in the pulmonary capillary pressure suggests that lymph flow plays a major role in the defense of the lung against edema.

MAGNO<sup>23)</sup> studied the effect of lymphatic ligation (the thoracic duct as well as the right lymph duct) on the change in lung water at elevated pulmonary pressures. Chronic lymphatic ligation increased the rate of water accumulation in the lung while acute lymphatic ligation caused accumulation of pleural fluid. It is interesting to note that, while lymphatic ligation, either chronic or acute, increased fluid, the chronic one reduced tissue safety factors.

In the author's experiment the gross findings of the removed lung after bilateral cervical vagotomy showed an edematous appearance, hemorrhage over the surface of the lung, and a little foam poured out of the trachea, while microscopic findings stained with hematoxyline and eosin showed dilated and hemorrhaged capillaries, inflammatory cells, thickened alveolar walls, interstitial and intra-alveolar fluid.

These findings seem to resemble those of the lung of ARDS<sup>1)2)30)</sup> (adult respiratory distress syndrome) which recently has attracted much attention, and of shock lung. From his hundred clinical cases of ARDS, BLAISDELL<sup>3)</sup> described that the lung resembles the liver in appearance because of the decrease in air content.

At first the lung was hemorrhagic and then became white grey in color and edematous in feature, and in microscopic changes variable numbers of fibrin and platelet microemboli filled pulmonary arterioles and later there was intra-alveolar congestion, hemorrhage or edema of alveoli. Four or five days later, these changed into hyaline membranes. But these were all nonspecific findings, thus it seemed difficult to diagnose from the pathophysiological findings.

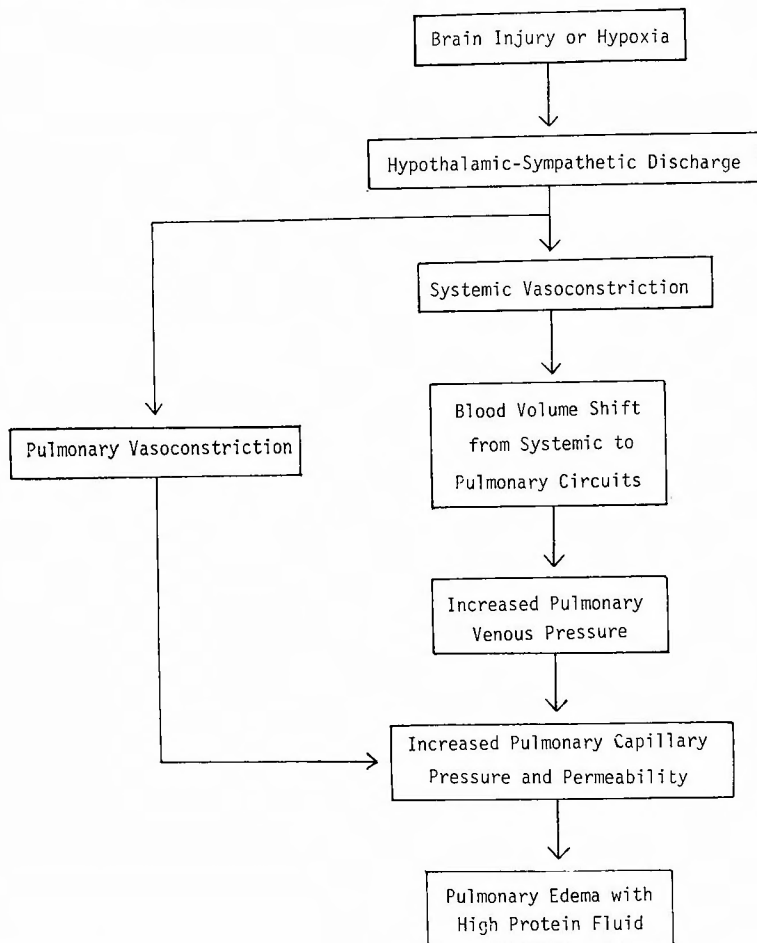
WILSON<sup>50)</sup> investigated in detail electromicroscopically shock lung at the cell level. And he described a group of pathologic findings that consist of the following: 1) massive vascular congestion, 2) pulmonary edema (both interstitial and intra-alveolar), 3) pulmonary hemorrhage (both interstitial and intra-alveolar), 4) hyaline membrane formations, 5) pulmonary fibrosis (if the patient survives for weeks or months after the initial injury). Moreover he discussed the pulmonary cellular response to shock.

KARLINER<sup>15)</sup> described, regarding pulmonary edema of shock lung, that blood corpuscle components and plasma protein infiltrated into the interstitial space by increased pulmonary capillary permeability, and then were transported in alveoli, to develop eventually pulmonary edema.

Generally, in pulmonary edema due to shock lung, the capillary permeability increases with leakage of fluid into the interstitial and intra-alveolar spaces. And this type of edema usually remains within the pulmonary parenchyma and does not infiltrate into the tracheo-bronchial tree.

PEMBERTON<sup>31)</sup> described two clinical cases with the pulmonary edema fluid (PEF)

Table 8 Development of neurogenic pulmonary edema. (Theodore)



evacuated from the endotracheal tube.

MOSS<sup>27)</sup> suggested that the central nervous system was concerned with the pulmonary circulatory system of shock lung. He perfused the central nervous system through one cannula in the dog's carotid artery. He was able to produce pulmonary edema or shock lung in the animals studied by simply producing cerebral hypoxia using anoxic blood with a  $\text{PaO}_2$  of 35 mmHg and normal blood flow and pressure. These experiments supported the hypothesis that brain injury in the form of cerebral hypoxia produced a massive sympathetic discharge that caused pulmonary edema or shock lung. He explained that massive increase in pulmonary circulatory volume by systemic vasoconstriction resulted in pulmonary edema. THEODORE<sup>43)</sup> provided an explanation of the mechanism of neurogenic pulmonary edema (Table 8).

The pathogenesis of neurogenic pulmonary edema is such that injury to the brain from either head trauma or shock with cerebral hypoxia stimulates hypothalamic sympathetic

discharge. This massive neural discharge is mainly an adrenergic impulse that produces systemic arterial vasoconstriction with a shift of blood volume from systemic to pulmonary circuits and increased pulmonary venous pressure.

This rapid change in pulmonary venous pressure and blood volume produces a great increase in pulmonary capillary pressure and permeability; it results in pulmonary edema with exudation of high protein fluid into the lung parenchyma.

### Conclusion

Postoperative pulmonary complications frequently occurred in patients operated for cancer of the upper two-thirds of the thoracic esophagus. In the majority of cases the main lesions were located in the anterior wall of the esophagus near the bifurcation of the trachea and they definitely invaded the adventitia or the neighboring structures.

These facts seem to suggest that injury of branches of the vagal nerve and of the posterior pulmonary plexus and interruption of the pulmonary lymph flow play important roles in the occurrence of the postoperative pulmonary complications. The author obtained the following experimental results of pulmonary changes in guinea pigs after bilateral cervical vagotomy.

1) After vagotomy the respiration became slow and deep, and the forced inspiration was gradually increased. From 90 minutes onward, foam poured out of the nose and the mouth and the guinea pigs died three or four hours after vagotomy. When the tube was previously inserted into the trachea by tracheotomy, the forced inspiration was very mild. But about 120 minutes later, the foam poured and the animals died at last four or five hours after vagotomy.

2) A gradual increase in the water content of the lung by EATON's method was observed to begin developing 90 minutes after vagotomy. The value 180 minutes after vagotomy was  $85.8 \pm 0.47\%$ , remarkably increased as compared with that of the control group ( $78.78 \pm 0.29\%$ ). Change in the water content of the lung was proved to be much less in winter than in summer. Some guinea pigs survived more than 12 hours in winter.

3) As for gross findings, the lungs became congested severely as time went on and they became remarkably hemorrhagic from about 90 minutes after vagotomy. And the lungs were deep red and edematous, apparently resembling the liver. The foam in the trachea also increased as time went on. In microscopic findings of the lungs stained with hematoxyline and eosin, alveolar spaces were slightly dilated and acidophilic fluid was seen in the alveoli from about 60 minutes after vagotomy. The inflammatory cells were moderately infiltrated into the enlarged alveolar septa, and there were some places which became atelectatic. Furthermore, dilated capillaries and a slight extravasation of the red cells were noted in the alveolar walls.

4) Arterial  $O_2$  tension at 30 minutes after vagotomy was  $44.28 \pm 4.01$  mmHg showing a remarkable drop from the pre-vagotomy value of  $86.28 \pm 4.39$  mmHg.  $PaCO_2$ , on the other hand, showed a tendency to rise after vagotomy but it was not statistically significant.

5) In fluorohistological findings using FITC dextran, FITC dextran was observed within the alveolar vessels in the control group. From 60 minutes after vagotomy, it infiltrated from the alveolar vessels into the interstitial. The dextran concentration increased significantly from 90 minutes after vagotomy.

6) The water content of the lung was not changed in the group of unilateral vagotomy alone. In the group of vagotomy on one side and electrical stimulation on the other, the water content of the lung increased as the power became stronger, but it had a converse tendency to decrease when the power was more than 0.5 mV. Also in the group of vagotomy on one side and electrical stimulation at both stumps, there was no significant difference as compared with the control group.

7) There were no significant changes in the water content of the lung of the group with bilateral cervical sympathectomy.

In the group in which bilateral sympathectomy was done at the same time as bilateral vagotomy, there was no difference in the water content of the lung as compared with the vagotomized group.

In the group in which bilateral sympathectomy was done 30 minutes before vagotomy, the water content of the lung significantly increased as compared with that of any other group.

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## 和文抄録

食道癌術後肺合併症の検討：とくに  
迷走神経と肺合併症との関連

## 第2編 実験的検討

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臨床的検討から、上・中胸部食道癌手術例、とくに癌病巣が気管分岐部の高さの前壁を中心に局在し、外膜浸潤が強度であった症例において、術後肺合併症が多発したことにより、病巣摘出およびリンパ節郭清のさいの迷走神経細枝および後肺神経叢の損傷が、食道癌術後肺合併症の発生に関与する一因と考えられた。そこでモルモットにおいて迷走神経切離（以下迷切と略記）のさいの肺の病態生理を明らかにするために実験的検討を加え以下の結果を得た。

1) モルモットに両側頸部迷切を行うと、呼吸はやや深く緩和となり、次第に吸気性努力呼吸を呈し、90分頃より鼻孔や口腔より泡沫液を出し、3～4時間で死亡した。次に予め気管切開を施行し、気管内にチューブを挿入固定しておき、両側迷切を行うと、吸気性努力呼吸は軽度となったが、120分頃より気管内挿入チューブより泡沫液の流出を認め、4～5時間で死亡した。

2) Eaton 法による肺水分量の測定を行うと、両側迷切後90分頃より肺水分量は次第に増加し、150分後には無処置群に比べて著明に増加した。なおこのさいの肺水分量は夏期より冬期において変化が少なく、また生存時間も長い例が多かった。

3) 両側迷切後の摘出肺の肉眼所見においては、時間の経過と共に充血の程度が増し、90分頃より出血の程度が強くなり、色調は褐赤色を呈し、水腫様となり、一見肝臓の外観を呈していた。気管内の泡沫液も時間と共に著明に増加していた。H・E染色による

組織像では、両側迷切後60分頃より毛細管拡張、軽度の出血、炎症細胞の浸潤などを認め、場所により Congestive atelectasis を認める部位もあり、肺胞壁は肥厚し、一部肺胞内に漏出液を認めることもあった。

4) 両側迷切後動脈血酸素分圧 ( $\text{PaO}_2$ ) は30分後にはすでに  $86.28 \pm 4.39 \text{mmHg}$  から  $44.28 \pm 4.01 \text{mmHg}$  と急激に低下していた。一方動脈血炭酸ガス分圧 ( $\text{PaCO}_2$ ) は時間と共にゆるやかに上昇する傾向を示したが、有意の差をもっては上昇しなかった。

5) FITC-DX (Fluorescein isothiocyanate dextran) を注入後の蛍光組織学的検索によると、無処置群では肺胞壁内に限局していたが、迷切後60分頃より次第に肺胞壁や肺胞腔内に漏出した。また肺胞壁や肺胞腔内へ漏出した dextran 量は迷切後90分より、無処置群に比して有意に増加していた。

6) 一側迷切のみでは肺水分量に有意の差を認めなかったが、一側を迷切し他側を種々の条件で電気刺激を加えて90分後の肺水分量をみると、出力の増加と共に水分量も増加し、0.5mV以上では逆に次第に減少する傾向を示した。

7) 両側交感神経切離では肺水分量に変化を認めなかった。また両側迷切と同時に交感神経を切離した群では、両側迷切群との間に差を認めなかったが、両側迷切30分前に交切を加えると、他のいずれよりも肺水分量は有意に増加していた。