EXPERIMENTAL STUDY ON PATHOGENESIS OF ACUTE POSTOPERATIVE PULMONARY EDEMA

by

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I. INTRODUCTION

Using the fat emulsion prepared in our laboratory in experimental animals and surgical patients, HIKASA et al.[1][2] have demonstrated that fat administration has a very favorable effect on protein, carbohydrate and fluid metabolism. It may be said that the significance of fat as a "variable element" (as a caloric source) has been almost completely clarified by their work.

However, since the classical discovery of BURR and BURR[3] that certain unsaturated fatty acids are essential for growth and, in fact, for survival, it has been generally recognized that fat has a much more important physiological significance as a "constant element" than as a "variable element".

Since the beginning of the administration of fat emulsion in patients undergoing various operations in our clinic, acute postoperative pulmonary edema (abbreviated as APPE) has almost completely disappeared. During the period 1956～1959, four patients of 24 undergoing radical operation for esophageal cancer and one patient undergoing operation for cardiac cancer developed APPE; none of these five patients had received fat emulsion. However, none of those receiving the emulsion (12 out of the 25 cases) developed APPE.

As seen from the data in Table 1, the incidence of APPE following radical operation for esophageal cancer is exceedingly high. Although various factors such as vagotomy, operative insult (especially that of thoracotomy), anoxia etc. have been blamed for this high incidence, there is no general agreement as to which the dominant factor is.[4]~[7] Patients with esophageal cancer are usually of a miserable nutrition because of both the restricted food intake due to dysphagia and the cancerous cachexia. Therefore, in order to gain success in operation, the nutritional

Table 1 Incidence of APPE following various operations

	Reporter	Number of patients	APPE	
			Number	%
Pulmonary resection for cancer	K. HAYASHI	31	4	12.9
Heart surgery	Y. YOSHIHARA	1053	34	3.2
Pulmonary resection for tuberculosis	M. TAKAHASHI	3829	87	2.2
Same as above	M. SHIOZAWA	981	5	0.5
Esophagectomy	A. WATANABE	393	159	40.5

state of the patients should be corrected by every possible means prior to the operation. As one of the available means, administration of the fat emulsion has been performed in our clinic; it has resulted not only in a marked improvement of the nutritional state of the patients but also in subsidence of APPE. These results suggest that the preoperative supply of nutrients is intimately related to the occurrence of APPE.

It is well known that the factors which contribute to the occurrence of APPE are very complex. ALTSCHULE[8] presented a table (Table 2) summarizing the etiologic factors of acute pulmonary edema. (It should be noted that since ALTSCHULE dealt with acute pulmonary edema in general, the factors enumerated there are somewhat different from those of APPE.) On the whole, numerous factors have been claimed to cause a rise in APPE, yet a definite one has not been obtained.

Table 2 Factors contributing to pulmonary edema

- I. Increased Transudation
  - A. Elevated capillary pressure in lungs
    - 1. Cardiac decompensation and mitral disease
    - 2. Venular constriction
      - a. Neurogenic
      - b. Histamine
  - B. Increased filtering area in lungs
    - 1. Increased blood volume
    - 2. Redistribution of blood
      - a. Peripheral vasoconstriction
  - C. Large blood flow in lungs
  - D. Lowered plasma protein level
  - E. Increased capillary permeability
    - 1. Anoxia
    - 2. Histamine ?
    - 3. Toxine
  - F. Bronchospasm
- II. Decreased Reabsorption
  - A. Impaired lymphatic function
    - 1. Elevated systemic venous pressure
    - 2. Inflammatory thrombosis ?
- III. Increased Total Extracellular Fluid Volume

Considering the fact that capillary permeability is controlled by the nutritional state especially of the essential fatty acids of the body, the author has postulated that deficiency of essential fatty acids causes an abnormal rise in the permeability of the lung capillaries and forms the background for the development of APPE. The present work was designed to test this hypothesis.

II. EXPERIMENTAL ANIMALS AND METHODS

A) Experimental Animals:

The rat has dietary habbits and a metabolism which are very similar to those of the human. Therefore, male albino rats of the WISTAR strain supplied by the Animal Center in Kyoto University were used for this study.

The weanling rats were divided into three groups: the first group was fed a synthetic diet practically devoid of fat, the second a synthetic fat-diet, and the third a rat chow (a product of ORIENTAL Yeast Ind. Co. Ltd. Japan). The weight composition of each diet is as follows. Fat-free diet: casein 20%, starch 76%, mixed salts 4% and vitamin mixture 0.6 g per 100 g of food.

Fat diet: casein 20%, sesame oil 15%, starch 61%, mixed salts 4% and vitamin mixture 0.6 g per 100 g of food. According to our colleague JINDO, each gram of the casein used in the study contained 1.39 mg of total lipids and 0.20 mg of

trienoic acid (fatty acids having three double bonds in a molecule, linolenic acid being one of these acids), and no other unsaturated fatty acids. Therefore, if a rat eats 10 g of the fat-free diet per day, the animal takes in essential fatty acids (abbreviated as EFA) in an amount less than 0.4 mg per day. The lipid content of the starch used was less than 0.01%, and the EFA content was not in the range of measurement.

As the source of EFA a purified and peroxide-free sesame oil was used; its linoleic acid content was 40.4%. Therefore, a rat eating 10 g of the fat diet daily takes in about 600 mg of linoleic acid per day. The weight composition of the rat chow is as follows: water 7.0%, protein 24.8%, lipids 5.6%, carbohydrate 51.4%, minerals 5.7% and others 5.6%. According to JINDO, the content of unsaturated fatty acids in the chow was as follows: dienoic acid 0.41%, trienoic acid 0.124%, tetraenoic acid 0.06%, pentaenoic acid 0.09% and hexaenoic acid 0.03%. Therefore, when a rat eats 10 g of the chow per day, the daily intake of EFA is less than 60mg.

B) Methods:

1) Capillary Resistance of the Abdominal Skin: The device[35] used in the experiments to test the capillary resistance consisted of a vacuum jar which was connected to an electrically powered suction pump on one side and to a small glass bell (of an inner diameter of 1.0 cm) on the other side. The degree of suction was measured by an intercalated mercury manometer. Suction was employed for 60 seconds. The least negative pressure given in cmHg still capable of producing hemorrhage was considered as the value of the capillary resistance. The capillary resistance was tested every week for a period of 9 weeks.

2) Papula Time (Time of Disappearance of Intradermally Injected Physiological Saline): Physiological saline in the amount of 0.1 cc was injected intradermally and the time of disappearance of the resulting papula was measured. The results of such a test, however, tend to be influenced by subjective impressions, therefore, the rate of disappearance of radioactivity was measured after the intradermal injection of radioactive phosphorus. A dilute physiological saline solution of radioactive phosphorus ($Na_2H\overset{*}{P}O_4$) was injected intradermally in the abdominal wall in the dose of 0.1 cc, and the radioactivity of the injected site was measured by a GEIGER-MÜLLER counter.

3) Water Test: The method is to be described later.

4) ANTU-Pulmonary Edema[9)10)]: Alpha-naphthyl thiourea was administered in doses of 3, 5, or 40 mg per kg and was injected intraperitoneally in an olive oil suspension, since it is practically insoluble in water. For all dosages each rat received 1 cc of olive oil suspension per 100 g of body weight. Just 4 hours after the injection of the drug, the rats were killed by bleeding and examined for pulmonary edema.

5) Wet Weight and Water Content of the Lung and Histological Examination:

Immediately after the pulmonary edema-provoking experiments, the rats were tied on their backs to a small operating board without any anesthesia.

The abdominal wall was opened and the vena cava and next the abdominal aorta were cut across allowing the blood to flow freely. After the blood flow ceased, the thoracic cavity was entered and a hemostat was placed just under the heart. The thoracic cavity was searched for pleural effusion. The left lung was dissected free and inspected for signs of edema or consolidation. Next, a ligature was looped around the lung and tied tightly at the hilum; a cut was made just proximal to the ligature. The surface of the lung was dried lightly on blotting paper before the organ was weighed. The same process was repeated with the right lung, which was fixed with a 10% formaline solution and examined histologically with hematoxylin-eosin staining. The left lung was dried for 72 hours in a dessicator at 70°C, and its water content was calculated by subtracting the dry weight from the wet. Rats which showed a consolidation of the lung probably due to pneumonia were excluded from the experiments.

The lung weight and water content of 24 normal rats maintained on rat chow and weighing 120～250 g are shown in Table 3. The proportionate lung weight (the lung weight as per cent of body weight) decreased as the body weight increased. The water content ranged from 76.2% to 80.8%. If over 80%, the presence of APPE should be suspected. The final judgment, however, was made on histological examination.

The proportionate lung weight and water content of three intact rats maintained either on the fat diet or on the fat-free diet for 6 weeks are shown in Table

Table 3 Proportionate lung weight and water content in normal rats

body weight	$\frac{\text{lung wt.}}{\text{body wt.}} \times 100(\%)$	water content (%)
120	0.88	78.3
125	0.79	78.4
130	0.78	80.8
135	0.52	77.1
140	0.53	76.4
140	0.58	79.3
150	0.65	76.8
150	0.60	76.2
155	0.77	76.3
160	0.77	77.3
160	0.71	79.1
170	0.72	78.4
180	0.62	78.9
200	0.64	79.7
200	0.71	79.6
225	0.65	77.2
230	0.67	78.4
230	0.56	76.5
235	0.66	78.2
240	0.60	76.8
245	0.59	76.2
250	0.61	77.5
250	0.58	78.0
250	0.59	77.6

Table 4 Proportionate lung weight and water content of each 3 intact rats fed either the fat diet or fat-free diet

Group	body weight	$\frac{\text{lung wt.}}{\text{body wt.}} \times 100$ (%)	water content
fat diet	160	0.54	77.7
	170	0.62	78.4
	190	0.51	77.8
fat-free diet	155	0.56	75.9
	170	0.56	78.0
	180	0.53	78.2

4; no significant difference was observed between these two groups.

III. RESULTS

A) Capillary Resistance and Permeability of the Abdominal Skin:

1) Capillary Resistance: The capillary resistance of 69 healthy weanling rats was measured and found to range rather widely as shown in Table 5.

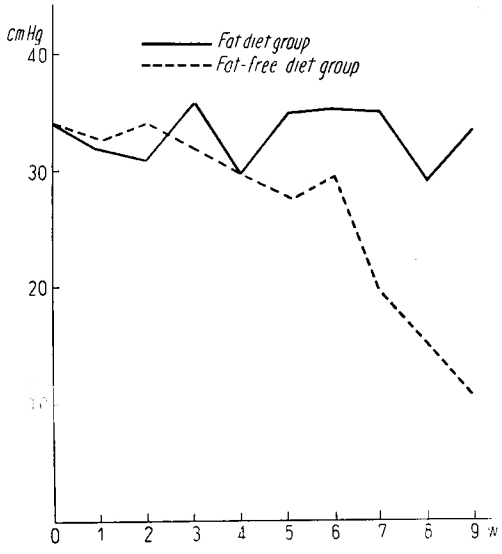
Table 5 Capillary resistance of weanling rats and of rats fed the fat-free diet or rat chow for 9 weeks

Capillary resistance in cmHg	Number of rats		
	weanling rats	fat-free diet	rat chow
>60	4	0	0
55	4	0	0
50	4	0	0
45	9	0	0
40	9	0	1
35	7	0	1
30	7	0	5
25	4	0	3
20	16	8	3
15	10	5	6
10	2	26	4
< 5	0	8	0

a) Capillary resistance of the fat diet group: Without exception the capillary resistance remained within the range of 25 to 40 cmHg, showing no fluctuations exceeding 10 cm of the original level found at the beginning of the experiments (Fig. 1).

b) Capillary resistance of the fat-free diet group: The capillary resistance maintained its original level during the first 4 weeks of the experiment, but began to decline between the fifth and sixth weeks. It then dropped to a low level (5~15 cmHg) at the ninth week and remained there for the rest of the experiment (Fig. 1 and Table 5). The gain in body weight of the rats also began to be slowed in accordance with the onset of the low capillary resistance.

Fig. 1 Change in capillary resistance during the course of experimental feeding



c) Capillary resistance of the rat chow group: The capillary resistance of the 23 rats fed rat chow for 9 weeks is shown in Table 5.

Fig. 2 Papula time of fat diet and of fat-free diet groups (Fach dot represents an individual rat.)

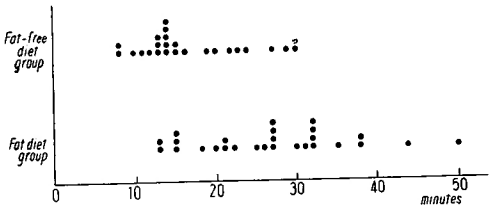
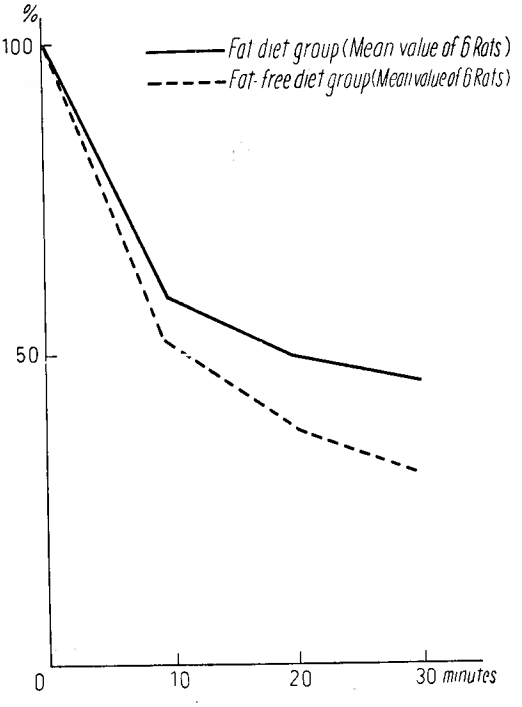


Fig. 3 Change in radioactivity after intradermal injection with radioactive phosphorus



2) Papula Time : The time of disappearance of intradermally injected physiological saline in rats fed either fat diet or fat-free diet for 9 weeks is shown in Fig. 2. Although it ranged rather widely as did the capillary resistance, the rats with a high capillary resistance were always found to have a long papula time.

The rate of disappearance of radioactivity after the intradermal injection of radioactive phosphorus was measured in 6 rats fed either the fat diet or fat-free diet for 9 weeks. The results are shown in Fig. 3.

All the above results reveal that the capillary permeability of the abdominal skin of rats fed the fat-free diet began to rise between the 5th and 6th weeks of the experimental feeding.

B) Water Test:

In the following experiments use was made of rats fed each diet for 9 weeks or more.

1) Single Administration of Water: Water equivalent to 5% of the weight of the rats was administered to 4 rats on the fat diet and 4 on the fat-free diet by stomach tube only once, and the urine volume of the rats was measured. As

Table 6 Urine excretion following single water administration

Group	No.	body weight	volume of the administered water (cc)	urine volume (cc) in 1.5 hr.	urine volume (cc) in 3 hrs.
fat diet	1	190	9.5	3	5
	2	205	10	2	4.5
	3	225	11	3.5	5.5
	4	190	9.5	1	3.5
fat-free diet	1	215	10.5	4	7.5
	2	230	11	1	3.5
	3	215	10.5	3.5	6.0
	4	230	11.5	2	4.5

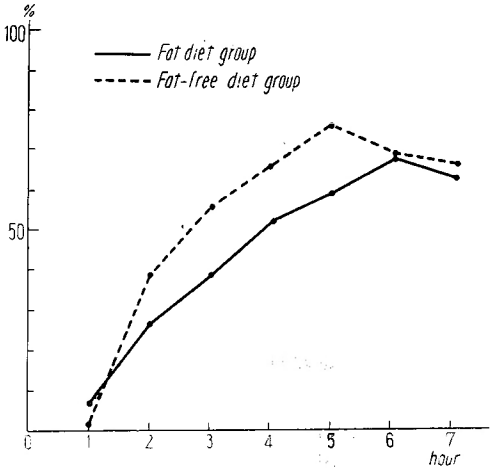
shown in Table 6, no difference was observed in the urine volume.

2) Repeated Administration of Water: The same amount of water was given repeatedly to 8 rats at hourly intervals seven times, and the hourly urine volume was measured. The rate of diuresis at a certain time was calculated from the following formula.

$$\frac{\text{Total volume of urine excreted}}{\text{Total volume of water ingested}} \times 100 \ (\%)$$

The results are shown in Fig. 4. The fat-free diet group showed maximum diuresis at the 5th hour, the fat diet group at the 6th hour. At the end of the experiments, however, the weight of the rats of both groups had decreased by about 5 g and no sign of water retention was observed.

Fig. 4 Urine excretion during the repeated water administration



These results revealed that the rats given water equivalent to 5% of their weight repeatedly at hourly intervals could excrete an equivalent volume of water, and developed no signs of water retention.

3) Inactivation or Excretion of Antidiuretic Substance (abbreviated as ADS): The ADS secreted from the thalamohypophyseal system under stress is believed to be inactivated by the liver. In order to examine whether the function of the inactivation was different between the fat diet and fat-free diet group, BIRNIE's test was performed in each group.[11)~14)]

i) Three rats from the fat diet and three from the fat-free diet group were selected for the test. The rats were injected with vasopressin (kindly supplied by TEIKOKU-ZOKI Pharmaceutical Co. Japan) in a dose of 0.25 unit subcutaneously two times with a two hour interval, and one hour after the last injection the rats were anesthetized with pentobarbital sodium. Then blood was collected from the vena cava and the serum was separated by centrifugation.

ii) Six intact rats maintained on rat chow were fasted for 12 hours (water was supplied ad libitum). Then the rats were given water equivalent to 5% of their weight twice with a one hour interval, then the animals were each injected with 1.5 cc of the serum obtained from the vasopressin-injected rats. Immediately thereafter, the rats were given the same amount of water only once. The volume of urine excreted by the animals during the experiments was measured at certain intervals.

iii) The ADS-BIRNIE value was calculated from the following formula.

$$\frac{C}{3A-B} \times 100 \ (\%)$$

A : The volume of water equivalent to 5% of the weight of the rats.
B : The volume of urine excreted before the third administration of water.
C : The volume of urine excreted during the 90 minutes following the injection of the serum.

The lower the value is, the greater the content of the ADS in the injected serum, that is, the slower the inactivation or excretion of the ADS in or from the body.

As seen from the results in Table 7, no significant difference in the inactivation or excretion of the ADS was observed between the fat diet and the fat-free diet group. Moreover, the rats injected with vasopressin at the above mentioned dose, both in the fat diet and fat-free diet groups, showed no recognizable change in physical condition.

Table 7 ADS-Birnie value

Group	No.	ADS-Birnie value (%)
fat diet	1	36.4
	2	56.2
	3	43.9
fat-free diet	1	33.2
	2	57.1
	3	40.3

C) Water-Vasopressin Test:

1) Experiment I: Five rats of the fat diet group, two of the fat-free diet group and four of the rat chow group were selected for the test. The rats were given water equivalent to 5% of their weight by stomach tube four times at hourly intervals, and were simultaneously injected with 0.25 unit of vasopressin subcutaneously twice with a two hour interval. (The experiment was arranged to simulate the postoperative state.) Although in all the rats the urinary excretion was suppressed markedly, signs of water intoxication were much more serious in the fat-free diet and rat chow groups than in the fat diet group. The former without exception developed respiratory distress, nasal bleeding and general convulsions and died, while the latter developed only mild convulsions but no nasal bleeding and survived the experiments (Table 8). Histologically the lungs of the former group showed typical pulmonary edema including intraalveolar transudation (Photo. 1, 2, 3), while the lungs of the latter showed no sign of pulmonary edema except for slight congestion of the capillaries.

Table 8 Water-vasopressin test (I)

Group	No.	urine volume in 3 hours (cc)	survival	$\frac{\text{lung wt.}}{\text{body wt.}} \times 100$ (%)	water content (%)
fat diet	1	12	survived	0.66	76.9
	2	6.5	〃	0.67	78.7
	3	7	〃	—	—
	4	5	〃	—	—
	5	5.5	〃	—	—
fat-free diet	1	10	died at 3°16′	1.46	82.9
	2	5.5	3°5′	1.11	85.4
rat chow	1	3.5	3°50′	1.19	89.1
	2	5	3°35′	1.37	89.4
	3	3.5	4°10′	0.60	77.5
	4	4	3°30′	1.12	85.0

Since no significant difference was observed in the urine volume of the rats in each group, the above difference observed between the fat diet group and the fat-free diet and rat chow groups in the response to the water-vasopressin test should be considered to be caused by the difference either in the water-distribution in the body or in the extrarenal water excretion. As evident from the study of PANOS and SINCLAIR,[15][16] however, the fat-deficient rat has a defective skin and an increased metabolic rate because of the deficiency of EFA, and has an increased water excretion from the skin. Therefore, the difference in water distribution should be considered the only causative factor. In order to test this concept, the following experiments were performed.

Five rats of the fat diet and five of the fat-free diet group were given water equivalent to 5% of the body weight three times and injected with 0.25 unit of vasopressin twice. Then the animals were killed by bleeding and the water content of their lungs, livers and gastrointestinal tracts were compared. As seen from the results in Table 9, although the water content of the liver and gastrointestinal tract

Table 9 Water content of lung, liver and intestine of rats killed by bleeding after administration of water 3 times and vasopressin 2 times

Group	No.	body weight (g)	water content (%)			urine volume in 3 hours (cc)
			lung	liver	intestine	
fat diet	1	270	79.1	68.2	76.8	3
	2	230	77.5	76.5	80.2	3
	3*	270	75.5	70.7	74.5	4
	4	280	74.7	—	—	8
	5	220	79.4	—	—	2
	6	245	78.2	—	—	5
fat-free diet	1	245	84.0	76.0	79.3	10.5
	2	140	80.5	71.4	79.4	4
	3*	185	77.6	71.3	76.1	6
	4	220	82.2	—	—	11
	5	215	82.2	—	—	11
	6	250	80.0	—	—	13

* : The rats administered with cortisone.

was almost the same in the two groups, that of the lung of the fat-free diet group was much greater than that of the fat diet group.

Especially Nos. 1, 4 and 5 showed typical signs of pulmonary edema including intraalveolar transudation (Photo. 4). Moreover the volume of urine excreted during the experimental periods was even larger in the fat-free diet group. These results indicate that in the fat-free diet group the perorally administered water was transported more rapidly from the intestine to the blood stream, extracellular tissue spaces and lastly into the tissue cells.

2) Experiment II: It was demonstrated in Experiment I that rats on the fat diet were much more resistant to the water-vasopressin test than the rats on the fat-free diet or on rat chow. In the following experiment, the effect of the administ-

ration of fat for relatively short periods of time was examined. Healthy rats were maintained on rat chow for about 9 weeks and then fasted for certain periods (water was supplied ad libitum), and 20% sesame oil emulsion equivalent to 5% of body weight of the rats was given by stomach tube once a day during the fasting periods. Control rats were given the same volume of 50% glucose solution. The rats thus treated were given water and vasopressin in the same way as in Experiment I. The results shown in Table 10 show that the administration of sesame oil emulsion for relatively short periods afforded a remarkable resistance against the water-vasopressin test (The larger amounts of water required by the fasted rats until their deaths may have been due to the dehydration caused by the fast.).

3) Effects of Cortisone on the Water-Vasopressin Test: Cortisone has been considered to be somewhat effective in the treatment of APPE, and was found by SCHILLER et al.[17] to have a preventive effect on water intoxication. The effect of cortisone on the water-vasopressin test was studied in the following experiments. Rats fed the fat-free diet for 9 weeks were injected with cortisone (5 mg of predonine), and 12 hours later were given water and vasopressine in the same manner as described in the previous experiments. The results, shown in Table 11, revealed that cortisone prevented water intoxication rather markedly. Next, the rats on both the fat diet and fat-free diet were treated with cortisone and their tolerance

Table 10 Water-vasopressin test (II)

	urine volume (cc) in 4 hours	urine volume (cc) in 7 hours	survival
A) Rats fasted for 24 hours			
i. infused with sesame oil emulsion 2 times	4	—	survived
ii. infuesed with 50% glucose solution 2 times	1	—	died at 5 hour
B) Rats fasted for 3 days			
i. infused with sesame oil emulsion 3 times	6.5	23	survived
ii. infused with 50% glucose solution 3 times	7	30	died at 8 hour
C) Rats fasted for 7 days			
i. infused with sesame oil emulsion 7 times	4	29.5	survived
ii. infused with 50% glucose solution 7 times	9	19.5	died at 8 hour

Table 11 Effect of cortisone on water-vasopressin test

Group	No.	urine volume in 3 hours (cc)	survival	water content of the lung (%)
fat-free diet not treated	1	10	died at 3° 16′	82.9
	2	5.5	〃 3° 5′	85.4
	3	9.0	〃 4° 10′	83.6
	16	6.0	〃 3° 10′	85.2
fat-free diet treated with cortisone*	14	5.5	survived	—
	15	9.0	〃	—
	6	10	〃	—
	7	8.5	〃	—

* Cortisone was administered in a dose of 5 mg 12 hours before the water-vasopressin test.

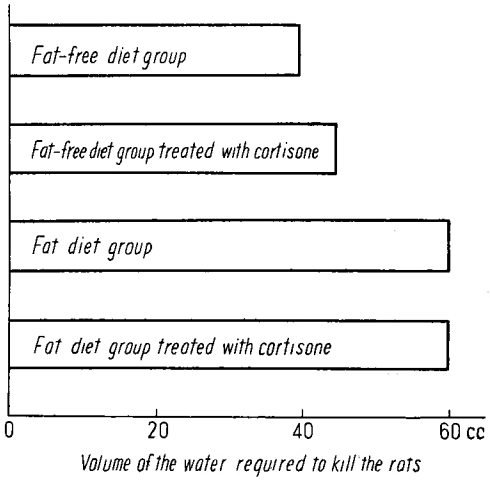
Table 12 Tolerance to water-vasopressin loading of the rats treated with cortisone

Group	No.	body weight (g)	water	vasopressin
fat diet	1	220	6 times	3 times
	2*	210	7**	4
	3*	220	6	3
fat-free diet	1	185	4	2
	2*	185	4	2
	3*	230	5	3

* : Rats administered with 5 mg of cortisone.
** : The rat died during the 7th administration of water.

to water-vasopressin loading was compared with that of rats not treated with cortisone (Table 12 and Fig. 5).

Fig. 5 Tolerance to water-vasopressin loading of the rats treated with or without cortisone



D) ANTU-Pulmonary Edema :

1) ANTU-Pulmonary Edema : Six rats were fed the fat diet and six the fat-free diet for a month and then injected with ANTU, 40 mg per kg ; four hours later the animals were killed by bleeding and their lung weight and water content were measured (Table 13). The rats of both groups showed without exception a great increase in lung weight and water content, and marked signs of pulmonary edema histologically (Photo. 5, 6). Even when the rats were given only 3 mg of ANTU, which was probably the least dosage to provoke pulmonary edema, both groups developed pulmonary

Table 13 Pulmonary edema following ANTU administration

Group	No.	body weight (g)	$\frac{\text{lung wt.}}{\text{body wt.}} \times 100$ (%)	water content (%)
fat diet (1 month) ANTU 40mg/kg	1	140	0.72	80.5
	2	175	0.93	83.5
	3	165	0.78	81.9
	4	160	0.89	80.8
	5	140	0.74	80.8
	6	140	0.79	82.7
fat-free diet (1 month) ANTU 40mg/kg	1	110	0.87	78.9
	2	180	0.79	82.2
	3	155	0.83	83.1
	4	135	0.67	81.1
	5	140	0.76	80.6
	6	125	0.69	81.5

fat diet (2 months) ANTU 3 mg/kg	1	305	0.93	83.7
	2	275	1.00	81.6
	3	305	0.97	82.5
fat-free diet (2 months) ANTU 3 mg/kg	1	260	0.85	80.0
	2	290	0.97	80.8
	3	280	0.71	79.6

Table 14 Urine excretion following administration of ANTU and water equivalent to 5% of body weight

Group	ANTU (mg/kg)	body weight (g)	urine volume (cc)			
			1 hr.	2 hrs.	3 hrs.	4 hrs.
fat diet	3	235	0	3	6	8
	3	290	0	2.5	5	10
	5	290	0	2.5	died	—
	5	255	0	1.5	0	—
fat-free diet	3	245	2	9	10	16
	3	255	3.5	6	10	12
	5	300	0	11	16	—
	5	250	2	12	12	—

edema to almost the same degree (Table 13).

2) Anuria Produced by ANTU[18]: ANTU induces water accumulation in the lung and pleural cavity. Therefore, when the drug is given along with water, the urine excretion of the animals should be restricted in accordance with the greater accumulation of water in the body.

Immediately after the injection of 3 or 5 mg of ANTU, the rats were given water equivalent to 5% of the body weight by stomach tube at hourly intervals, and the urine volume was measured hourly. As shown in Table 14, the rats on the fat diet showed even more marked anuria and pulmonary edema.

IV. DISCUSSION

Tomioka,[19] in our laboratory, has demonstrated that when dogs were subjected to profound hypothermic anesthesia, the animals given 20% sesame oil emulsion daily for about one week showed less increase in blood viscosity and hematocrit value than the controls (Figs. 6 and 7). As is well known, abnormally low body temperature induces paralytic dilatation and increased permeability of capillaries. The hemoconcentration caused by these mechanisms burdens the circulatory system and is one of the defects of profound hypothermic anesthesia. The observations of Tomioka revealed that the administration of the fat emulsion for a relatively short period prevented not only the hemoconcentration but also the occurrence of ventricular fibrillation. Our colleague Kobayashi[20] observed that the administration of the emulsion in dogs before and after gastrectomy maintained the blood colloidal osmotic pressure and the volume of the extracellular and intracellular fluid at near the normal level even in the postoperative state. Tamaki[21] observed the same facts in

Fig. 6 Change in blood viscosity during profound hypothermic anesthesia

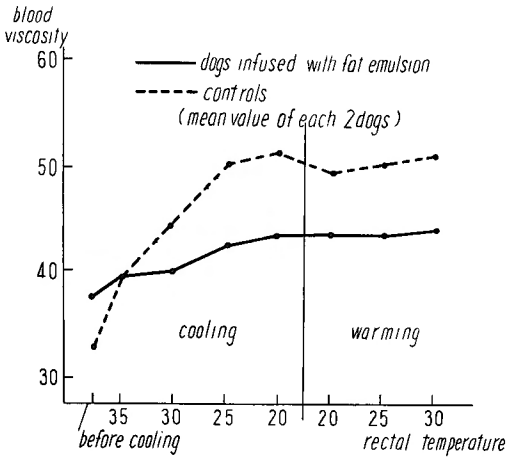
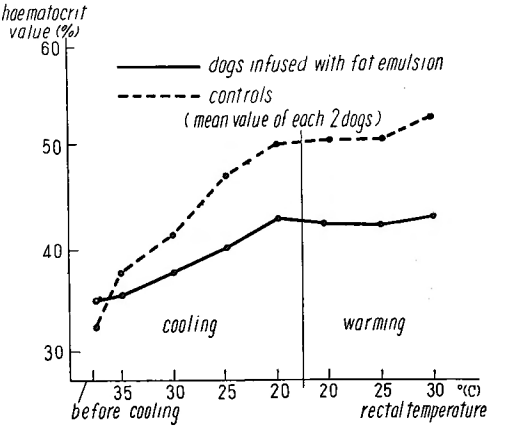


Fig. 7 Change in haematocrit value during profound hypothermic anesthesia



gastrectomy patients. These effects should be attributed not only to the protein sparing action of the fat emulsion demonstrated by our colleagues OSA,[22] KUYAMA[23] and HANAFUSA,[24] but also to its effect in preventing increased capillary permeability.

These results and the clinical observations mentioned in the Introduction led us to the assumption that the incidence of APPE was influenced by the nutritional state especially by the EFA-status of patients.

BURR and BURR in 1929, for the first time, listed the fat-deficiency syndrome in rats as follows: (1) marked retardation in growth; (2) development of scaly skin and caudal necrosis; (3) kidney lesions with concomitant hematuria; and (4) death. The specific nutritional significance of fat especially that of EFA has been investigated by numerous workers,[25][26][27] and it has been demonstrated more clearly that fat has a very important significance as a constant element in the body.

The unsaturated fatty acids which are classed with these so-called "essential fatty acids" are linoleic acid, linolenic acid and arachidonic acid. These three fatty acids all have the structure $-CH=CH-CH_2-CH=CH-$ in common, and the fatty acids having this structure were formerly considered to have the function of EFA. Recently, however, MEAD et al.[28] have demonstrated that the trienoic acid found in large amounts in the organs of fat deficient rats is not linolenic acid but 5, 8, 11-eicosatrienoic acid. This acid, though having the structure $-CH=CH-CH_2-CH=CH-$, has no function as EFA. MONTAG et al.[29] have postulated that this acid comes from the oleic acid family rather than from the linoleic and linolenic acid families.

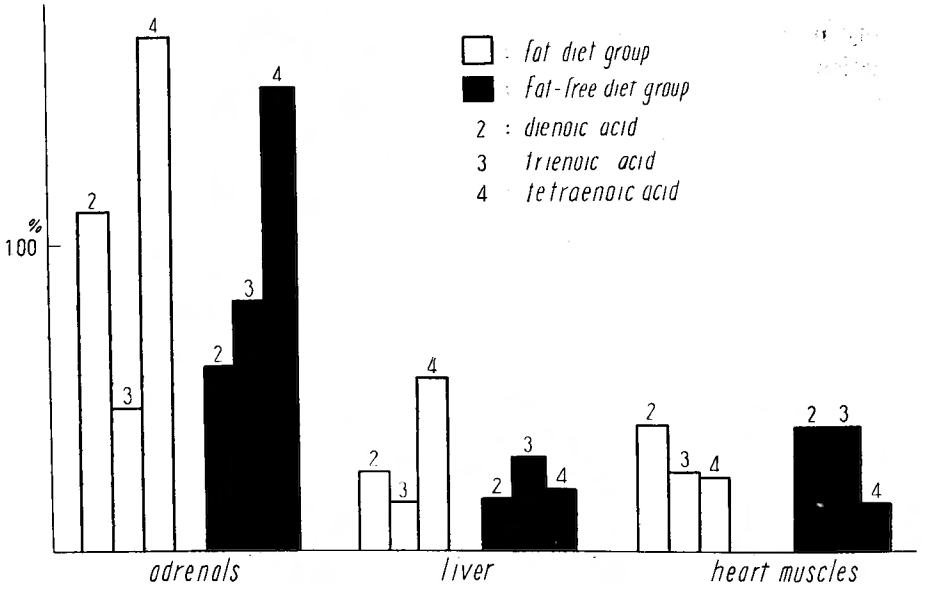
There is no general agreement as to the optimum dosage of EFA required by rats. BURR and collaborators[26] cited the figure of 40 mg of linoleic acid as the optimum dosage per day. More recently the DEUEL group[25] has placed the figure for linoleate requirement even higher than 100 mg for male rats.

Although the three fatty acids are classed as EFA, according to TURPEINEN[30][31] et al. the principal unsaturated fatty acids required by the animal organism is arachidonic acid, and it has been demonstrated by numerous workers that arachidonic

acid can come from linoleic acid in the animal organism in the presence of vitamin B_6.[32]

Since, in the present study, the rats fed the fat-free diet received EFA at a level less than 0.4 mg per day as previously mentioned, they naturally developed EFA-deficiency in the course of the feeding. The fatty acid composition of the liver fat of the rats fed the fat-free diet for 6 weeks was studied chromatographically by TOBE in our laboratory, and was compared with those of the rats fed the fat diet or rat chow. As seen in Photograph 7 the rats fed the fat-free diet showed the lightest spot of linoleic acid of the three groups. Moreover the unsaturated fatty acid content in the adrenals, liver and heart muscles of the rats fed the fat-free diet for 9 weeks was studied by JINDO. As seen from the results shown in Fig. 8, the rats fed the fat-free diet showed a marked decrease of dienoic acid and an increase of trienoic acid. These results agree completely with those obtained by AAES-JORGENSEN[33][34] et al.

Fig. 8 EFA contents in various organs of the rats fed either fat diet or fat-free diet



The capillary permeability of these fat-deficient rats was tested by measuring the capillary resistance and the time of disappearance of intradermally injected physiological saline, and was found to be abnormally increased.

KRAMÁR,[35] performing the same experiment as that of the author, observed that increased capillary permeability of the fat-deficient rats was restored to normal within two weeks by administration of linoleic acid.

Increased capillary permeability of the abdominal skin does not necessarily indicate increased permeability of the capillaries of the whole body, especially of the lungs. However, the change caused by a deficiency of diet is naturally considered to be prevalent in the whole body. The observations that the fat-deficient rats developed much more serious water intoxication and pulmonary edema indicate that the

capillary permeability of the lung of the fat-deficient rats increased abnormally in parallel with the increase in that of the abdominal skin.

As is well known, EFA take part in the formation of phospholipids; cell membranes are rich in phospholipids which are considered to be part of the lipoprotein complex.[36] Therefore, it is rational to believe that EFA play an important role in maintaining the normal permeability of cell membranes and capillaries as one of their structural components. SINCLAIR,[27] pointing out the structural function of EFA, ascribed to the deficiency of EFA many of the fat-deficiency syndromes such as increased fragility of the erythrocytes, increased skin permeability and evaporation, mitochondrial changes,[37] dissociation of oxidative phosphorylation, and elevated oxygen consumption and basal metabolic rate.[38]

The author has demonstrated in the present study that EFA-deficiency induces structural changes and increased capillary permeability, and produces a background for the development of APPE.

The observations that fat-fed rats developed rather serious pulmonary edema following ANTU administration would also indicate that fat is a constituent of cell membranes and capillary walls. The fact that the drug is practically insoluble in water and has to be administered as a suspension in olive oil suggests that it may have an affinity for lipids, and easily invade the lipoprotein contained in the capillary walls and thus increase their permeability. Therefore it is rational to believe that the fat-fed rats develop more serious pulmonary edema because of the high content of lipoprotein in their capillary walls. Moreover, these observations suggest that ANTU-pulmonary edema can hardly simulate the clinical acute postoperative pulmonary edema, since the mechanism of ANTU-edema differs greatly from that of the clinical one.

Next, cortisone was demonstrated to have a preventive action against water intoxication, affirming the observations of SCHILLER et al. In the "Textbook of Endocrinology" THORN et al.[39] stated: "The 11, 17-oxygenated corticoids, such as hydrocortisone and cortisone, maintain cellular hydration at the optimum, preventing both excessive dehydration and water intoxication." KRAMÁR et al.[40][41][42] demonstrated that the glucocorticoids played an important role in maintenance of the normal capillary permeability. Therefore, cortisone is believed to ameliorate the increased capillary permeability due to EFA-deficiency and to prevent water intoxication.

As is well known, the adrenal cortex contains a large amount of lipids, which are mainly composed of cholesterol (especially esterified cholesterol) which is considered to be a precursor of adrenal hormones. And, in general, cholesterol must be esterified with EFA for normal metobolism.

Moreover, our colleagues, MAKI and JINDO, with paper chromatography and isomerizing methods respectively, have demonstrated that the adrenals of rats, dogs and rabbits contain a large amount of EFA (Photo. 8). HOLMAN and GREENBERG[43] previously demonstrated that the testes and ovaries contained a relatively large amount of EFA. From these observations it has been postulated that EFA have a

very important role in the synthesis and metabolism of steroid hormones.[44)45)] Our colleague MATSUDA[46)] studied the changes in the liver glycogen content and histological changes in the adrenals when rats were fasted for a period. According to his study, rats fed a low fat diet, though showing an earlier onset of the neogenesis of liver glycogen, developed an carlier decrease and finally exhaustion of liver glycogen and succumbed to starvation much earlier than rats fed a high fat diet. Moreover, the adrenal cortices of the rats fed low fat diets showed loss of lipid granules (sometimes accompanied by the appearance of gross lipid granules), hyperemia or bleeding, cytolysis etc., while the organs of the high fat diet rats preserved the lipid granules fairly well and failed to show the so-called "exhaustive changes" (These changes were observed mainly in the zona fasciculata, and were few in the zona glomerulosa.). These findings also suggested that EFA play an important role in the synthesis or metabolism of adrenal hormones. Recently SINCLAIR[45)] declared: "If cholesterol must be esterifed with EFA the same might be true of closely related sterols. In deficiency of EFA in the rat there is greatly increased sensitivity to vitamin D, perhaps because it is normally esterified with EFA and accumulates if esterified with more saturated fatty acids or transisomers.

Table 15 EFA content in the adrenals, liver and heart muscles of normal rabbits (percentage in organ weight)

	Adrenals	Liver	Heart muscles
Total lipids	15.09	5.25	3.08
Dienoic acids	1.33	0.91	0.70
Trienoic acids	0.84	0.19	0.15
Tetraenoic acids	1.03	0.17	0.08

The relationship of EFA to steroid hormones has hardly been investigated. EFA occur abundantly in adrenal cortices, testes and ovaries, and they may be concerned with the synthesis of steroid hormones from cholesterol, or with the metabolism of steroid hormones (such as the esterification of the hydroxyl on C_{21} in cortisone or hydrocortisone), or both. This field we started to explore, and it may well be fruitful". We are also now investigating the changes in the 17-hydroxycorticosteroid content of the urine and blood of EFA-deficient animals, the changes in EFA content of the adrenals in response to stress etc. Even the results obtained in our laboratory up to this time, however, are sufficient to indicate the intimate relationship between EFA and the adrenals.

Our impression is that the ability of the adrenal cortex to synthesize hormone is impaired by EFA-deficiency. Therefore, the adrenals of the EFA-deficient animals cannot respond sufficiently to the increased hormonal demand of the organism subjected to such stresses as infection, operative insult and trauma. This phenomenon we speak of as "decrease of adrenocortical capacity."

SAYERS[47)] has criticized SELYE's idea of "Exhaustion" declaring that the adrenal cortex of healthy animals cannot be exhausted as a result of its hyperfunction. However, if the gland were deprived of a part of the enzymatic complement or material necessary for synthesis of its hormones, it would seem reasonable to suppose

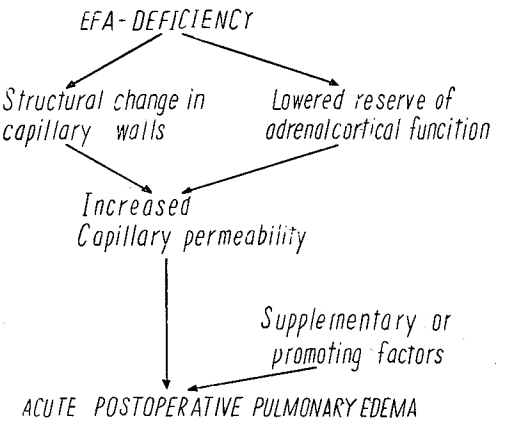
that exhaustion could occur in meeting a normal or an increased demand for hormones. The reasonableness of the concept was proved, for example, by the studies of WINTERS,[48] HURLEY[49] and DUMM[50] on the adrenal coritical function of pantothenic acid-deficient rats.

Increased capillary permeability has long been considered a typical change after bilateral adrenalectomy. The findings of hemoconcentration (ATHANASIN and GRADINESCO, 1909), increased protein in the lymph (COPE, BRENIZER and POLDERMAN, 1942), augumented spreading of intradermally injected pigment (OPSAHL, 1949) and increased capillary fragility (KRAMÁR, 1953) after bilateral adrenalectomy have been regarded as evidence of increased capillary permeability. Moreover, it was reported by KRAMÁR[40] that the increased capillary permeability due to ether anesthesia, operative insult (sham adrenalectomy) and adrenalectomy could be restored by cortisone, but not by ACTH or DOCA.

It is evident from these observations that adrenal hormones, especially glucocorticoids, maintain normal capillary permeability and suppress its abnormal increase due to stress. Moreover, KRAMÁR observed that after ether anesthesia and sham adrenalectomy capillary permeability began to increase after the fourth day and returned to its original level after two or three weeks, but after adrenalectomy it began to increase as early the second day and remained permanently low. These results indicate that the organism began to suffer from deficiency of adrenal hormones about four days after ether anesthesia and sham adrenalectomy, and more rapidly after adrenalectomy. The fact that capillary permeability due to a stress increases not immediately but a few days after the stress suggests that adrenal hormones are consumed during this period, and the hormone producing or secreting capacity of the adrenal cortex is finally exceeded by the demands of the body. These results are the more interesting in view of the clinical fact that APPE frequently occurs a few days after operation.

On the whole, the causes of the high incidence of pulmonary edema in fat-deficient (EFA-deficient) rats could be summarized as follows. EFA-deficiency, on the one hand, induces deficiency of the lipoprotein constituent of tissue cells and provokes structural changes and therefore increased capillary permeability, and on the other hand decreases the adrenocortical capacity to render it impossible to suppress the increased capillary permeability. These changes all together form a background for the development of APPE. If a promoting factor such as overhydration be added, then APPE develops. The above concept is summarized in Fig. 9.

Fig. 9 Mechanism of acute postoperative pulmonary edema



EFA are contained in all the tissues of the animal body in a constant amount and play an important role in the growth and reproduction of tissues. Malignant neoplasms, of course, consume EFA largely because of their elevated metabolism and rapid growth.[51][52] Therefore patients with esophageal cancer would frequently suffer from EFA-deficiency due not only to decreased intake but also to increased consumption of EFA.

The incidence of APPE following radical operation for upper and middle esophageal cancer is higher than that following operation for lower. Some authors ascribe this to vagotomy at a high level. However, it can also be attributed to a larger operative insult and higher frequency of overhydration. Moreover, the operation for lower esophageal cancer, in which the interference of vagotomy is probably neglected, can also provoke APPE, if the preoperative nutritional state is poor and the postoperative treatment inadequate. We have, in fact, had a patient with cardiac cancer, who died of APPE two days after total gastrectomy by laparotomy only. Moreover, the higher incidence of APPE following operation for pulmonary cancer than for pulmonary tuberculosis can be accounted for not only by the larger operative insult but also by the undernutrition and EFA-deficiency due to the cancer.

The author, of course, does not intend to exclude miscellaneous factors such as anoxia, nervous factors etc. in the development of APPE but considers them as supplementary and promoting factors.

In the meantime, a simple expansion of extracellular fluid cannot account for the very serious and rapidly developing symtoms of APPE, and a rapid expansion of intracellular fluid should also be given consideration. As previously mentioned, the permeability of the cell membranes of EFA-deficient animals increases abnormally as a result of the structural defects and lowered adrenocortical capacity. Therefore it was postulated by the author that the rapid expansion of intracellular fluid due to both the increased permeability of cell membranes and overhydration was the most important factor in APPE. Further studies on this point, for example electronmicroscopy, are awaited.

V. SUMMARY

A 20% sesame oil emulsion prepared in our laboratory has been given to surgical patients and has proved to be effective in improving nutrition. It was also noted that administration of the emulsion prevented APPE. The mechanism of this effect was studied in these experiments.

Recently the nutritional significance of fat not only as a caloric source but also as a source of EFA has been more clearly recognized. EFA are constituents of lipoprotein which is a structural component of tissue cells, and EFA-deficiency induces increased permeability of cell membranes and of capillaries.

It was confirmed by the present study that in EFA-deficient animals permeability of capillaries and cell membranes was increased.

EFA were found in large amounts in the adrenal glands of rats, dogs and rabbits and were postulated to have an intimate relationship with synthesis or meta-

bolism of adrenal hormones. Therefore, the EFA-deficient animals probably have a lowered adrenocortical capacity and cannot respond to the increased demand of adrenal hormones due to stress.

The stress usually induces an abnormal rise of capillary permeability, which is suppressed by the adrenal hormones secreted in large amounts following the stress. However, if the adrenocortical capacity is decreased, the amount of cortical hormones secreted is insufficient to suppress the increased capillary permeability.

Therefore EFA-deficiency induces: 1) structural changes in cell membranes and increased capillary permeability; 2) decrease of adrenocortical capacity; and 3) forms the basis for the development of APPE. Patients with esophageal cancer tend to be deficient in EFA because of both the prolonged restriction of food intake and the increased consumption of EFA, and therefore are prone to APPE. From these points of view, it is easy to understand why APPE occurs frequently following operation for esophageal and pulmonary cancer, why cortisone is more or less effective in the treatment of APPE, and why anoxia, overhydration, vagotomy etc. cannot by themselves provoke a definite pulmonary edema.

As is well known, APPE usually develops very suddenly and rapidly, and the recognition of its onset or early diagnosis is quite difficult. Moreover, no available treatment of decisive superiority for the disease is at hand. Therefore it is most important to prevent the disease by every available means. The preoperative improvement of the nutritional state, of water and electrolyte balance, of the function of the circulatory and respiratory systems etc. have, in fact, resulted in a decreased incidence of APPE. However, since EFA-deficiency, as revealed by the present study, forms a background for the development of APPE, the preoperative administration of fats rich in EFA in patients undergoing surgery should be considered as one of the most effective ways of preventing APPE.

VI. CONCLUSION

The mechanism of APPE was studied and the following conclusions were reached.

i) The EFA-deficient animal has an increased capillary permeability.

ii) The EFA-deficient animal easily develops water intoxication and pulmonary edema following overhydration.

iii) Cortisone suppresses the increased capillary permeability and therefore more or less prevents APPE.

iv) Patients with esophageal or pulmonary cancer tend to be deficient in EFA both because of their decreased intake and of their increased consumption, and therefore are prone to APPE.

v) The mechanism of APPE is considered to be as follows. When patients who have abnormally constructed capillaries and decreased reserve of adrenal cortical function due to EFA-deficiency are subjected to an operation, the capillary permeability increases markedly. If these patients are given excessive water, they develop APPE.

vi) The prevention of APPE is most important at present, and it can be

satisfactorily accomplished by the amelioration of EFA-deficiency.

vii) EFA probably play an important role in the synthesis or metabolism of adrenocortical hormones, especially of glucocorticoids. In regard to this problem further studies are awaited.

The author wishes to express his sincere gratitude to Dr. Y. Hikasa, the lecturer of our clinic, for his helpful suggestion and kind guidance in the course of the work.

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和 文 抄 録

体内不可欠脂酸の欠乏と術後急性肺水腫の発生素因に関する実験的研究

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食道癌根治手術後に術後急性肺水腫が頻発し易く，而もゴマ油乳剤を投与することによつてその発生が殆ど完全に防止され得る臨床的事実に鑑みて，脂質代謝の異常が術後急性肺水腫の発生素因として極めて重要な意義を有するのではないかと考え，試獣を用いて次の諸実験を行い，術後急性肺水腫発生機序の解明に努めた．

即ち，ウイスター系雄ラッテを2群に分け，1群は合成無脂質飼料で，他の1群は15%ゴマ油含有合成飼料で夫々2～3ヵ月間飼育し，斯る両試獣群を以てその腹壁皮膚毛細血管抵抗値及び丘疹消失時間を測定し，また水分負荷＋Vasopressin 注射試験及びその際にコーチゾンを予め投与し，また更に当該試獣の各種臓器の不可欠脂酸含有量をも測定して両群の間にいかなる差異があらわれるかを検討し，次の結果を得た．

(1) 生体内不可欠脂酸の欠乏は皮膚毛細血管壁自体の構造的変化を招き，その透過性は著しく昂進することが判明した．

(2) 著者は自家考案の水分負荷＋Vasopressin 注射試験によつて不可欠脂酸欠乏試獣に臨床的にみられると全く同様の術後状態を人為的に再現することが出来，而も臨床的にみられる肺水腫と組織学的にも全く同一の実験的肺水腫を作製し得た．その際，皮膚血管透過性の昂進が著しい試獣ほど，強度の肺水腫像を呈した．従つて肺毛細血管の透過性自体の変化は直接実測することは不可能であつたが，この透過性と皮膚毛細血管透過性との間には相関性のあることが充分に考えられる．

(3) 無脂質食飼育によつて一旦毛細血管透過性が異常に昂進した試獣でも，それに比較的短期間ゴマ油を投与すると，毛細血管透過性は正常に復し，肺水腫の発生は抑制される．

(4) コーチゾンの投与は毛細血管透過性の異常昂進を抑制し，肺水腫の発生に対しても抑制的に作用した．併しその効果はゴマ油投与の効果には及ばなかつた．

(5) 各種正常動物の副腎には他の臓器に比べて遙かに大量の不可欠脂酸が含有されているものであるが，無脂質食飼育時にはこの不可欠脂酸含有量は特異な変動を示すようになる．

(6) 不可欠脂酸は副腎皮質機能と極めて密接な関聯性を有し，副腎皮質ホルモン殊に糖質コルチコイドの合成乃至代謝過程に大きな役割を演じている．

以上の結果から，一般臨床において認められる術後急性肺水腫の発生原因並びにその発生機序として考えられることは，即ち，生体内不可欠脂酸が欠乏すれば一方では血管壁自体の構造的変化を招き，他方には手術侵襲を契機として当然分泌されて毛細血管透過性の昂進を抑制するコーチゾンの分泌にも異常が起り，換言すれば副腎皮質機能予備力が低下するようになるので，かかるものに対し，手術侵襲が加えられると，毛細血管透過性は異常に昂進し，ために過剰給水が行われると肺水腫を発生し易くなるのである．而して，食道癌等のように術前既に著しい栄養の摂取制限が存在していて，更に癌腫の存在によつて不可欠脂酸消費量の著しく増大している様な際には，当然の結果として生体内の不可欠脂酸も著しく欠乏しており，従つてかかる個体にあつては既に術後急性肺水腫の発生素因が潜在しているものと考えて差支えない．

術後急性肺水腫の早期診断及び治療は現在なお極めて困難であるから，その発生予防手段を術前予め講ずることが極めて重要であつて，その目的の為には生体内不可欠脂酸欠乏状態を是正することが甚だ肝要である．

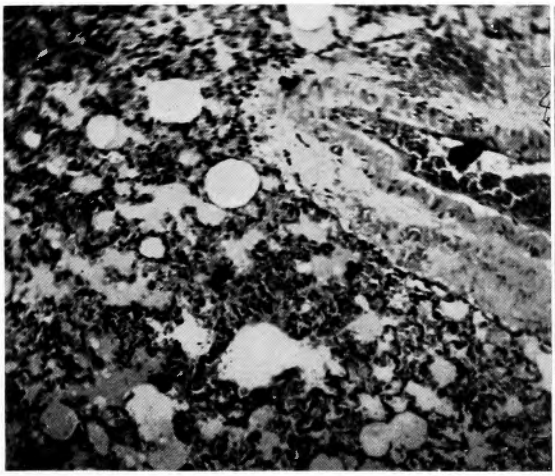

Photo. 1 Fat-free diet rat : Water 4, Vasopressin 2 times ; Water content 85.4%

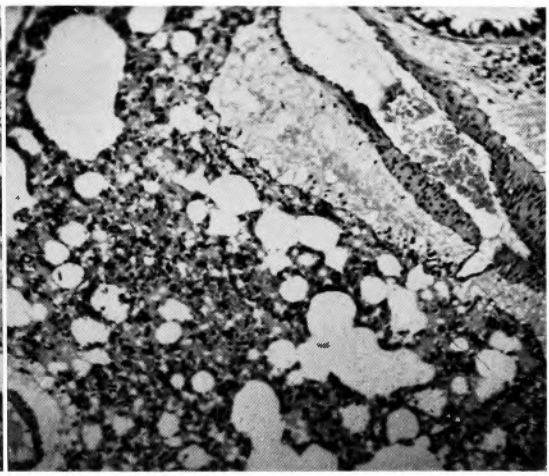

Photo. 2 Rat chow rat : Water 4, Vasopressin 2 times ; Water content 89.4%

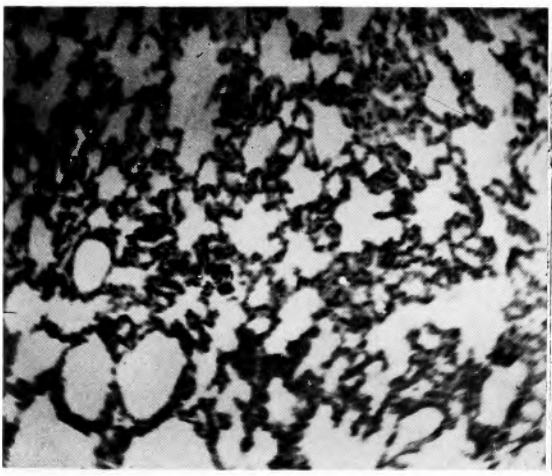

Photo. 3 Fat diet rat : Water 4, Vasopressin 2 times ; Water content 78.7%

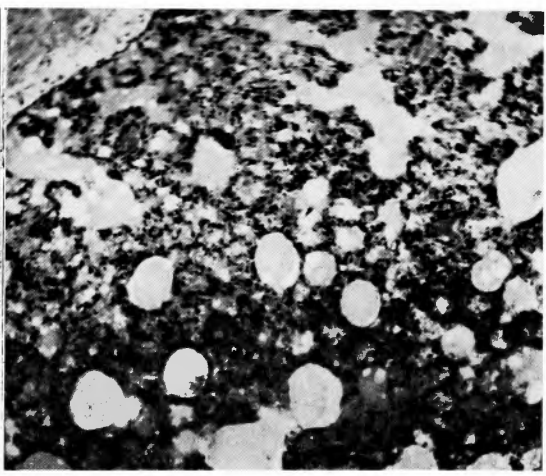

Photo. 4 Fat-free diet rat : Water 3, Vasopressin 2 times ; Water content 84.0%

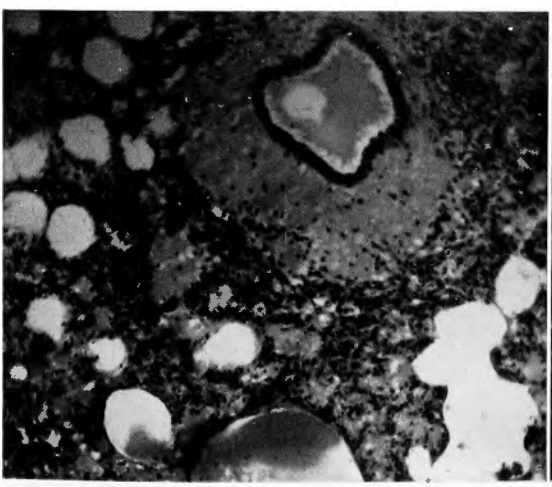

Photo. 5 Fat diet rat : ANTU 40mg/kg, Water content 83.5%

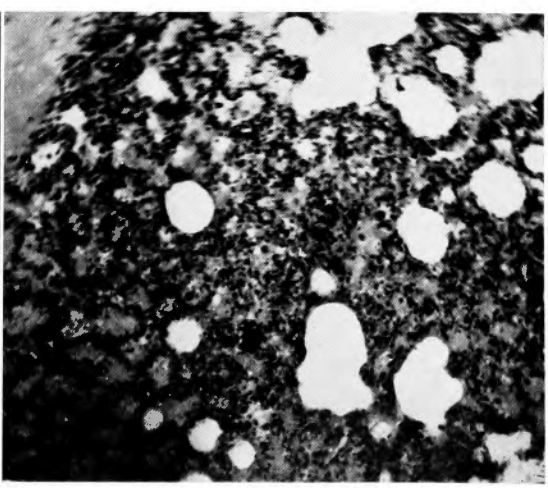

Photo. 6 Fat-free diet rat : ANTU 40mg/kg Water content 82.2%

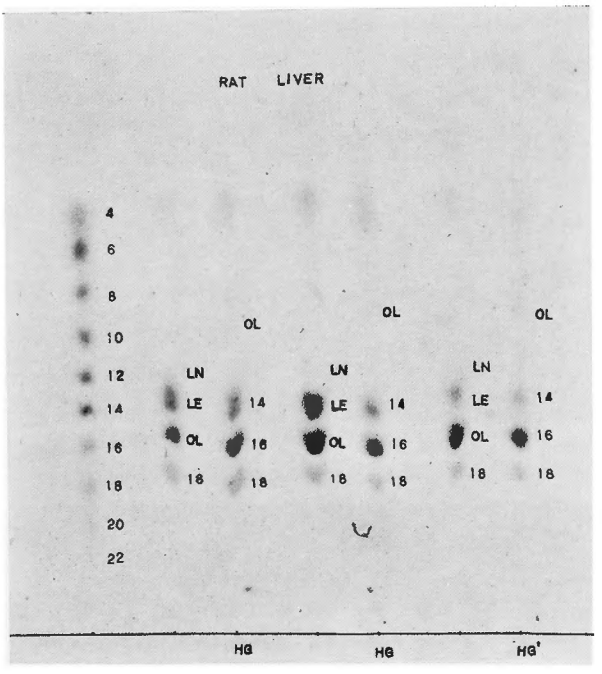

Photo. 7 Paper chromatogram of liver fatty acids
A : Rat chow rat
B : Fat diet rat
C : Fat-free diet rat

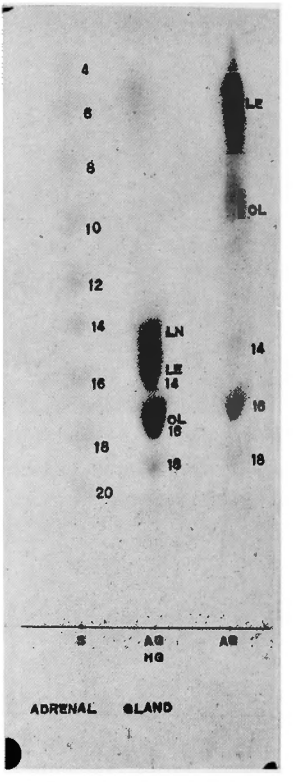

Photo. 8 Paper chromatogram of fatty acids of the dog adrenal

Electron Microphotographs of Pulmonary Edema
(photographed by our colleague M. YAMAGUCHI)

AE : Alveolar Epithelium
AL : Alveolar Lumen
BM : Basement Membrane
CE : Capillary Endothelium
CL : Capillary Lumen
R : Red Blood Cell
V . Vacuoles
W : White Blood Cell

Note that the capillary damage is more marked in ANTU-edema than in vasopressin-edema.

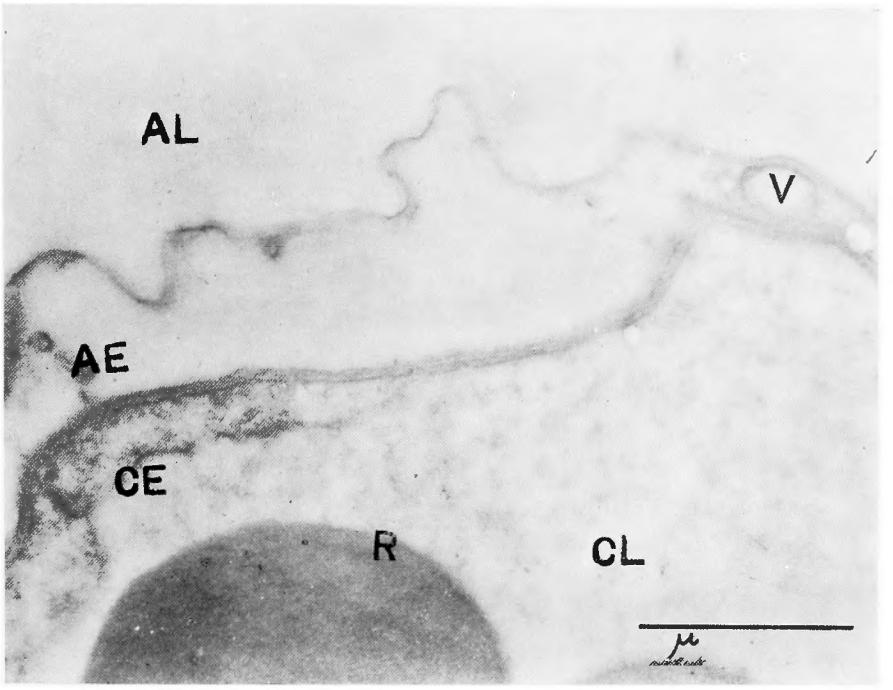

Photo. 9 Per oral water loading and subcutaneous administration of vasopressin. Both the alveolar epithelial cells and the capillary endothelial cells swell up, the latter showing less degree of change. These cells show also vacuolization. (×55,000)

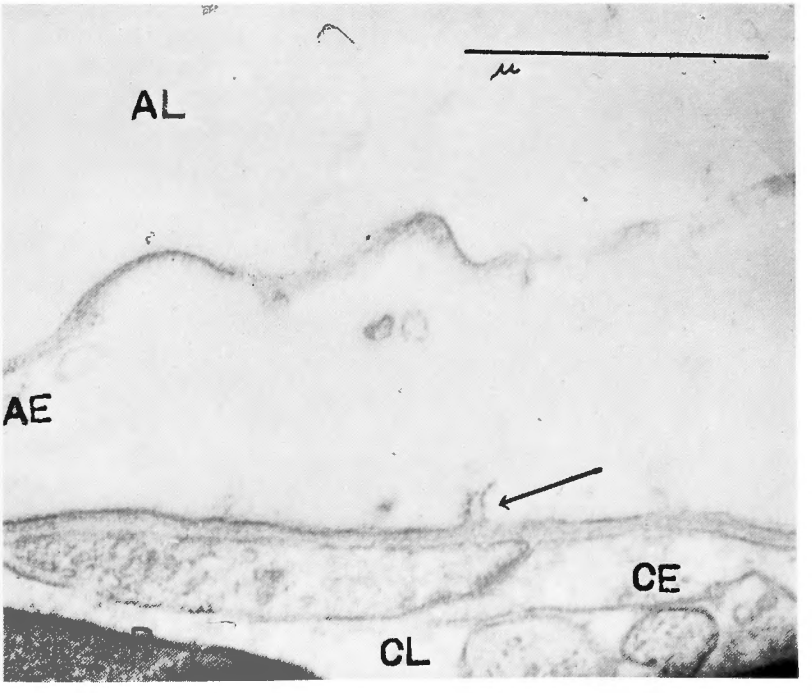

Photo. 10 Per oral water loading and subcutaneous administration of vasopressin. The arrow shows so-called "Schleusenartige Öffnungen der basale Membran des Alveolarepithels" by SCHULZ, which is the condition of extreme elevation of pinocytic activity due to destruction of the epithelial cell-membrane. (×73,200)

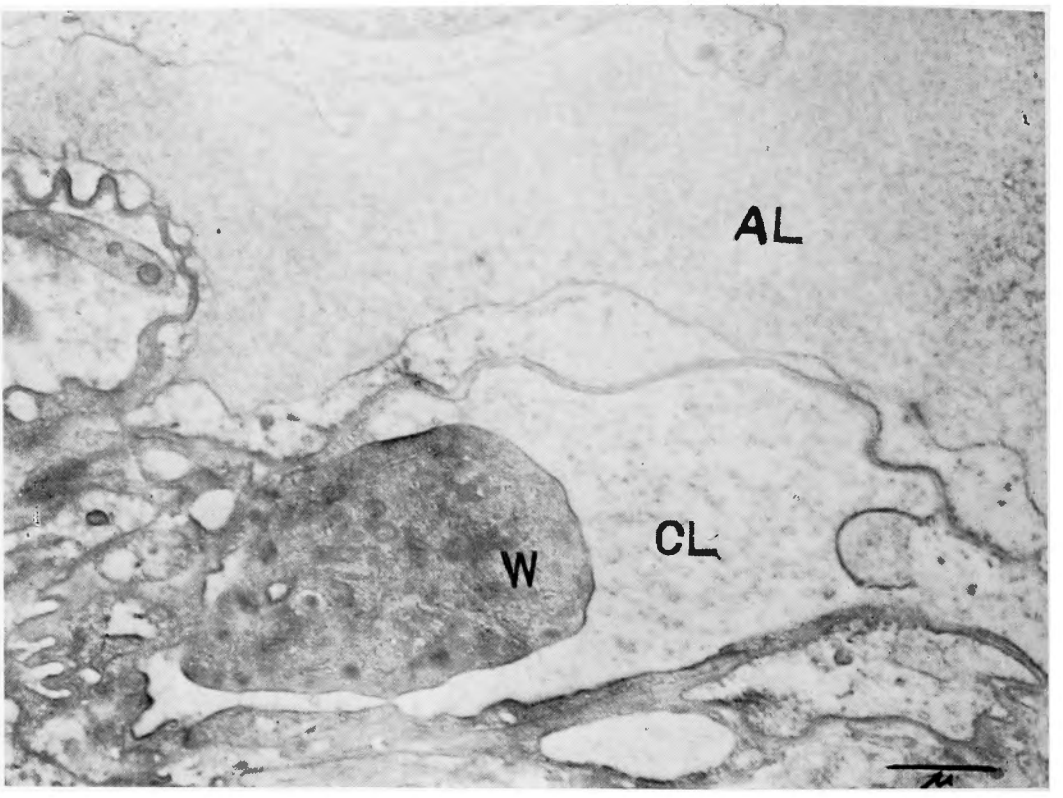

Photo. 11 Pulmonary edema induced by ANTU. Both the alveolar epithelial cells and the basement membrane shows wavy extension. Exuded materials in the alveolar cavity is homogenous and is higher in electron density than the capillary lumen. (×20,800)

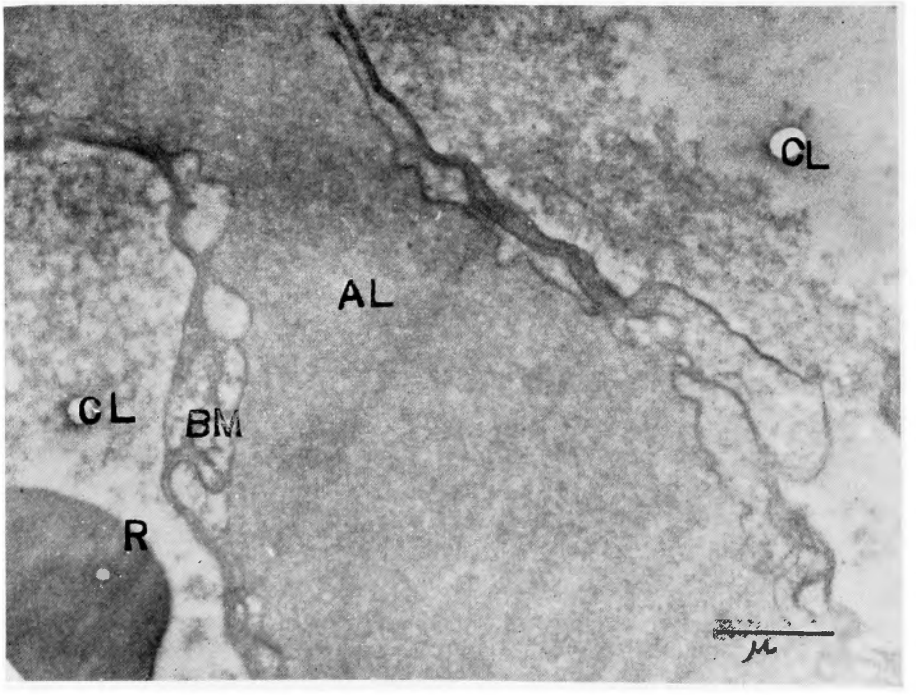

Photo. 12 Pulmonary edema induced by ANTU. In addition to the changes as described in Fig. 31, there is destruction of the capillary endothelial cells. (×20,800)