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Studies on the Process of Critical Movement of Intravascular Fluid into Intracellular Space

by

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I. INTRODUCTION

After the World War II, in parallel with a progress in chest surgery, incidence of acute postoperative pulmonary edema (abbreviated as APPE), which is one of the most serious postoperative complications, became more and more frequent. And APPE was one of the themes of the Annual Meetings of Japanese Association for Thoracic Surgery on 1958 and of Japanese Association for Surgery on 1960.

ALTSCHULE presented a table summarizing the etiologic factors of acute pulmonary edema and concluded that the fundamental disorder seemed to be a rate of transudation from the pulmonary capillaries that exceeded the reabsorptive capacity of the pulmonary lymphatics.

WAKIZAKA et al. have, on the basis of their extensive studies, concluded that impaired absorption of lymph is not of great significance as a causative factor of APPE, which develops very rapidly after operation.

Table 1 Factors contributing to pulmonary edema (ALTSCHULE)

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

URABE has classified APPE into three groups.

1. Postoperative pulmonary edema due to nerve lesion (cerebral operation or trauma, especially lesion of brain stem, pons and medulla).

2. Postoperative pulmonary edema due to abnormal cardiopulmonary hemodynamics: The patient with longstanding disturbance in pulmonary circulation is declined to develop APPE when hypoxia is induced by operation or by anesthesia and excess fluid is given.

3. Postoperative pulmonary edema which occurs in patients with hypoproteinemia, anemia and hepatic and/or renal insufficiency.

URABE has, from his clinical observations and histological studies, concluded that main causative factor of APPE of group 1 is pulmonary hypertension and increased capillary

permeability, that of group 2 is pulmonary hypertension, and that of group 3 is increased capillary permeability due to abnormal metabolic products.

Experimentally, he has produced each group of APPE by respective methods; group 1 by destruction of bilateral preoptic area and stimulation of the vagus and sympathetic nerve, group 2 by lung resection (decreased vascular bed in lungs) with resistance against inspiration, hypoxia and rapid infusion of large amounts of fluid, and group 3 by ANTU injection. And he has pointed out the great significance of nervous factor in pathogenesis of APPE.

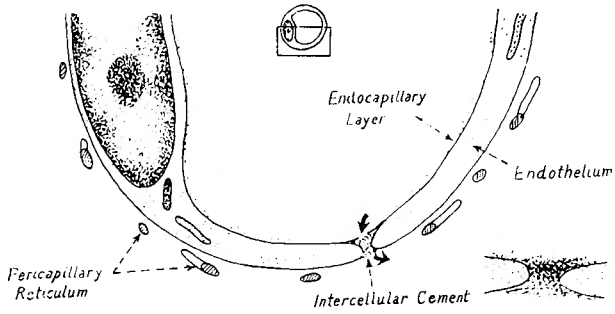
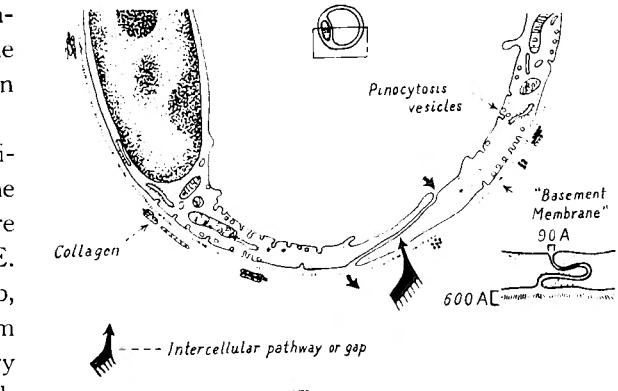


Fig. 1 Capillary wall (Traditional concept)



(FAWCETT)

Fig. 2 Capillary wall (Current concept)

SAKAKIBARA has, from his experience in heart surgery, indicated the elevated pulmonary capillary pressure as a main causative factor of APPE. In his experiment using heart pump, pulmonary capillary pressure of 40mm Hg was neccessary to cause pulmonary edema in normal dogs, whereas capillary pressure of 25mm Hg was enough in dogs with mitral stenosis. Moreover, electronmicroscopically the lungs of patients and dogs with mitral stenosis showed destruction of the capillary wall and extravasation of erythrocytes. From these observations, SAKAKIBARA has concluded that vascular bed of the lung of patients with heart diseases has a disposition to develop APPE.

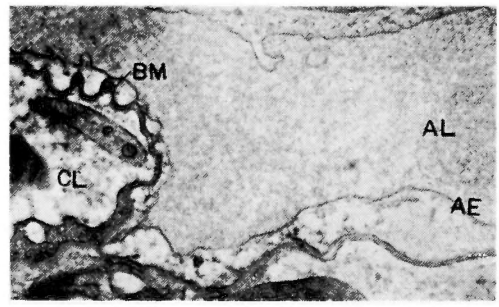


Fig. 3 Selective and destructive change (wavy extension) of basement membrane induced by ANTU injection (rat)

On the whole, numerous factors have been claimed to cause a rise in APPE, yet no definite one has been obtained. It is evident that APPE is caused not only by one factor but by many factors in combination.

In order to clarify how intravascular fluid moves into intracellular space, the structure of cell membrane and capillary wall must be given consideration.

II. PRESENT UNDERSTANDING OF STRUCTURE OF CAPILLARY WALL AND CELL MEMBRANE

Structure and permeability of capillary wall has been a subject of discussion from past up to present.

According to CHAMBERS and ZWEIFACH, the capillary wall has a structure as shown in Fig. 1.

Water and water soluble substance move through only intercellular cement, and lipophilic substances, O_2 and CO_2 move mainly through cell membrane. Therefore, the main factor which determines the capillary permeability to water is the porosity of intercellular cement.

Almost all of physiological phenomena can be explained reasonably by considering that the intercellular cement has many small pores of 30～50Å in diameter.

Recent electron microscopic study has, however, corrected CHAMBERS's theory, and according to FAWCETT, PALADE, POLICARD, KISCH, MOORE, RUSKA and others the structure of capillary wall should be as shown in Fig. 2. Capillary of all organs has, as mentioned later, definite intercellular pathway.

The basement membrane is a homogenous membrane of 500～600 Å in width, and its chief component has been considered to be mucopolysaccharides which is substratum of connective tissue in general. While the substratum of connective tissue, however, disappears during the process of making specimen for electron microscopy, the basement membrane stains densely with osmium and shows selective and destructive change by ANTU injection [ANTU is a lipophilic substance! (Fig. 3)]. Therefore, the basement membrane differs definitely from substratum of connective tissue and seems to be rich in lipids. Intercellular pathway of capillary wall is filled with same substance as basement membrane.

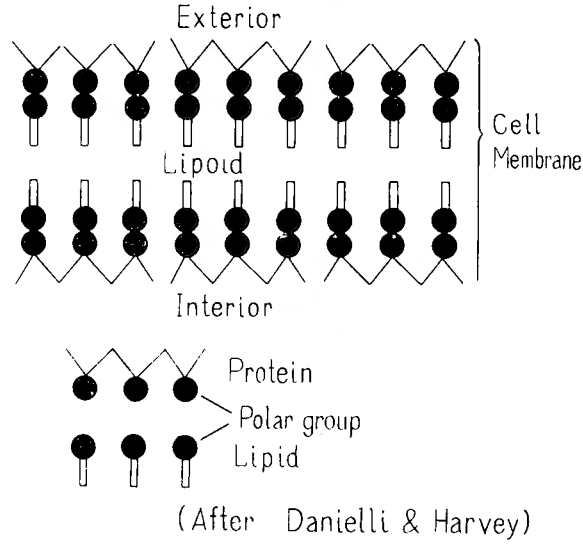


Fig. 4 Cell membrane

Cell membrane is composed of lipoprotein complex, and DANIELLI depicted a picture as Fig. 4.

In summary, all the basement membrane, cell membrane and intercellular pathway which determine the permeability to water are rich in lipids.

III. CRITICAL MOVEMENT OF EXTRACELLULAR FLUID INTO INTRACELLULAR SPACE

When animals are fed a diet deficient in essential fatty acids for a certain period of time, fatty acid con-

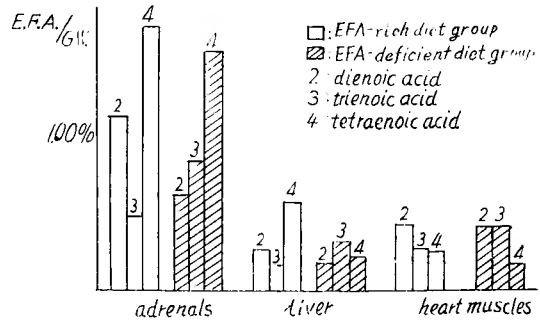


Fig 5 Polyenoic fatty acid content in various organs of organisms fed either EFA-rich diet or EFA-deficient diet.

tent in the organs shows a typical pattern of change, i. e. decrease in dienoic and tetraenoic acids and increase in trienoic acid (Fig. 5). Essential fatty acids (abbreviated as EFA) in the skin also show same change. In parallel with this change, insensible water loss increases remarkably. These facts indicate that capillary permeability of the skin increases markedly in EFA-deficient organism.

As is well known, the lung has the largest amount of collagenous tissue same as the subcutaneous tissue, and its tissue tension against extravasation of fluid is very low. Therefore, the lung develops edema more easily than the other organs. Moreover, since the pulmonary edema causes such serious signs and symptoms as bloody-foamy sputum and dyspnea, its occurrence can be detected earlier than that of the edema of the other organs. From these facts, we have studied the process of critical movement of extracellular fluid into intracellular space in lung. And we have performed an experiment to develop acute pulmonary edema by a new method—slow administration of water and antidiuretic hormone—with an intention to simulate the postoperative condition. Our colleague Dr. YAMAGUCHI has demonstrated by electron microscopic study that the acute pulmonary edema caused by a rapid infusion of an extraordinarilly large amount of fluid differs from clinical one, in that the edema is most remarkable rather in capillary endothelium than in alveolar epithelium. Therefore, in our experiment water was given per os in small amounts repeatedly in order to avoid rapid administration of fluid.

As shown in Tables 2 and 3, the EFA-deficient rats developed acute pulmonary edema following administration of water and antidiuretic hormone.

We studied the developmental process of this edema by electron microscopy. According to this study, the capillary of the lung also has the intercellular pathway. Although movement of water by pinocytotic vesicle (transport vesicle) cannot be denied, large parts of water passes through the intercellular pathway and moves into the alveolar epithelium, since the swelling of alveolar epithelium and forming of "schleusenartige Öffnungen" (destruction of cell membrane of alveolar epithelium) are found first near to the intercellular pathway (Figs. 6 and 7).

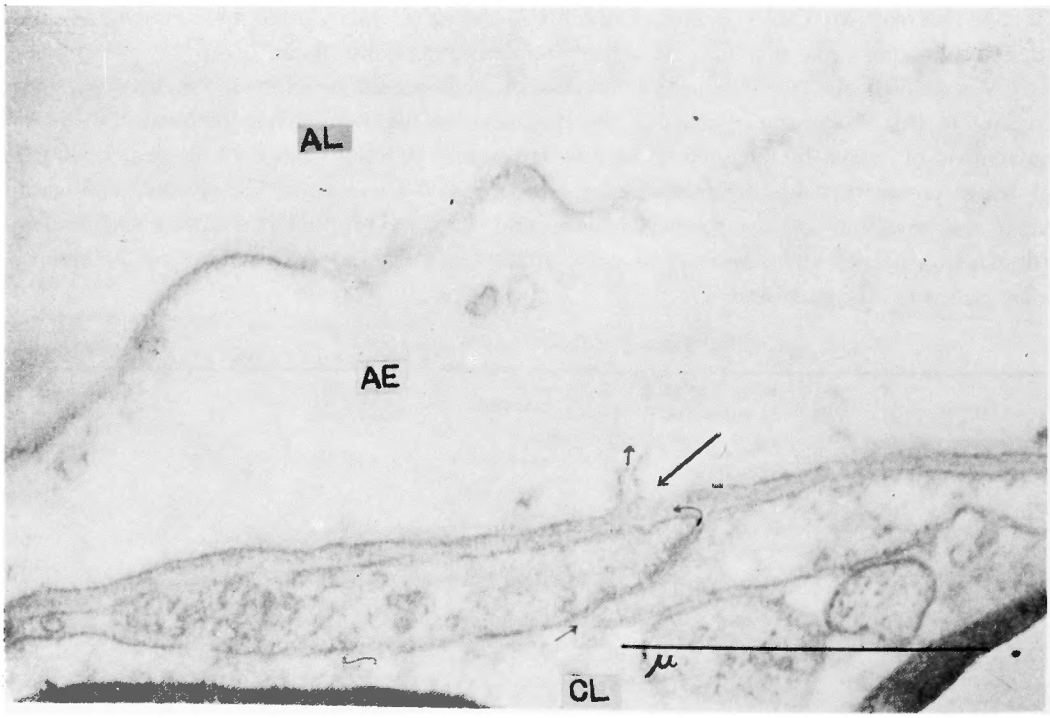
Table 2 Water-vasopressin test (I)

Group	No.	urine volume in 3 hours (cc)	survival	$\frac{\text{lung wt.}}{\text{body wt.}} \times 100$ (%)	water content (%)
EFA-rich diet	1	12	survived	0.66	76.9
	2	6.5	〃	0.67	78.7
	3	7	〃	—	—
	4	5	〃	—	—
	5	5.5	〃	—	—
EFA-deficient diet	1	10	diet 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	1°10′	0.60	77.5
	4	4	3 30′	1.12	85.0

Table 3 Water-vasopressin test (II)
(Water content of lung of rats killed by bleeding after administration of water 3 times and vasopressin 2 times)

Group	No.	body weight (g)	water content of lung	urine volume in 3 hours (cc)
EFA-rich diet	1	270	79.1	3
	2	230	77.5	3
	3*	270	75.5	4
	4	280	74.7	8
	5	220	79.4	2
	6	245	78.2	5
EFA-deficient diet	1	245	84.0	10.5
	2	140	80.5	4
	3*	185	77.6	6
	4	220	82.2	11
	5	215	82.2	11
	6	250	80.0	13

* : The rats administered with cortisone.

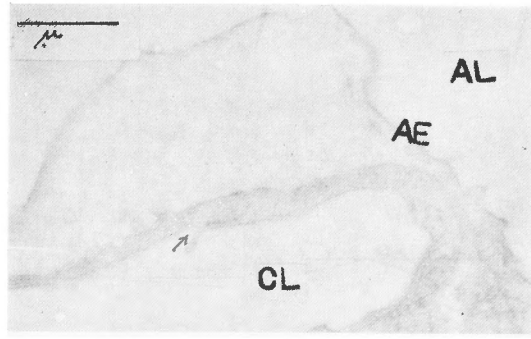


Large arrow shows so-called "schlousenartige Öffnungen." Small arrows show the process of critical movement of intravascular fluid into intracellular space through intercellular pathway.

Fig. 6 Critical movement of intravascular fluid into intracellular space (lung of EFA-deficient rat)
(AE : Alveolar epithelium, AL : Alveolar lumen, CL : Capillary lumen, BM : Basement membrane, CE : Capillary enothelium)

Our colleague Dr. KOBAYASHI has demonstrated that when the dogs deprived of essential fatty acids are gastrectomised and given excess water (physiological saline, 5 % glucose and RINGER's solution), the intracellular phase of body water increases rapidly, whereas in the intact animals only the extracellular water increases (Figs. 8, 9 and 10).

In summary, the basement membrane, intercellular pathway and cell membrane control the critical movement of water and essential fatty acids are essential component of all of them in common. Therefore, essential fatty acid deficiency causes increased capillary permeability and forms a background for the development of water-intoxication.



Arrow shows the intercellular pathway (gap).
The swelling of alveolar epithelium is found near to the intercellular pathway.

Fig. 7 Critical movement of intravascular fluid into intracellular space (lung of EFA-deficient rat)

IV. ESSENTIAL FATTY ACIDS AND ADRENOCORTICAL FUNCTION

The adrenal cortex contains the largest amount of essential fatty acids in the whole body, and in essential fatty acid deficiency dienoic and tetraenoic acids decrease and trienoic acid increases (Fig. 5).

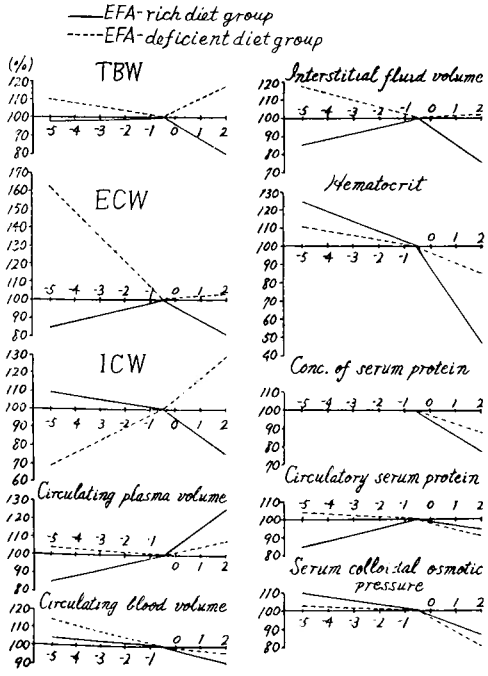


Fig. 8 Changes in fluid distribution in dogs which were infused intravenously with isotonic saline solution.

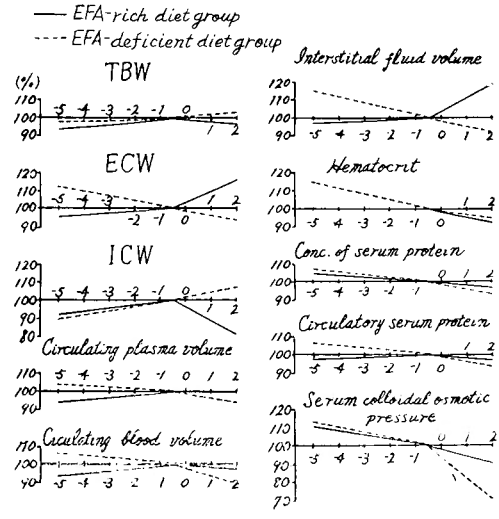


Fig. 9 Changes in fluid distribution in dogs which were infused intravenously with 5% glucose solution.

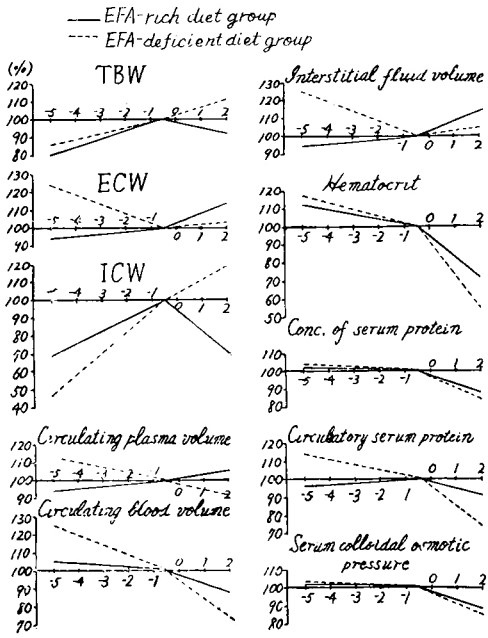


Fig. 10 Changes in fluid distribution in dogs which were infused intravenously with RINGER's solution.

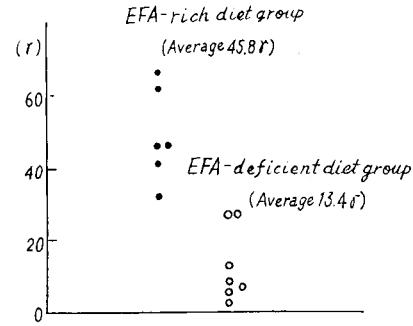


Fig. 11 Resting levels of urinary formaldehydogenic corticosteroids (rat).

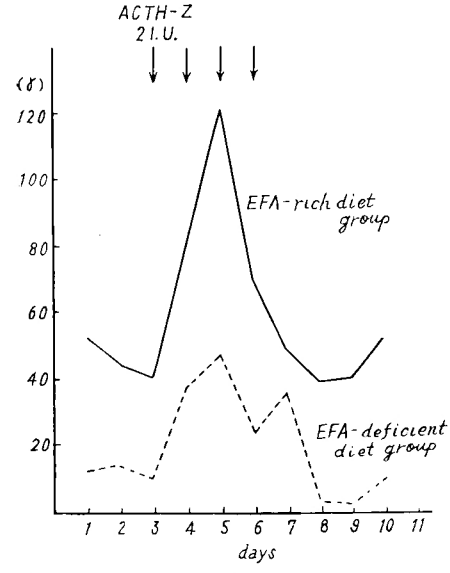


Fig. 12 Effect of ACTH-Z on urinary formaldehydogenic corticosteroid levels (rat).

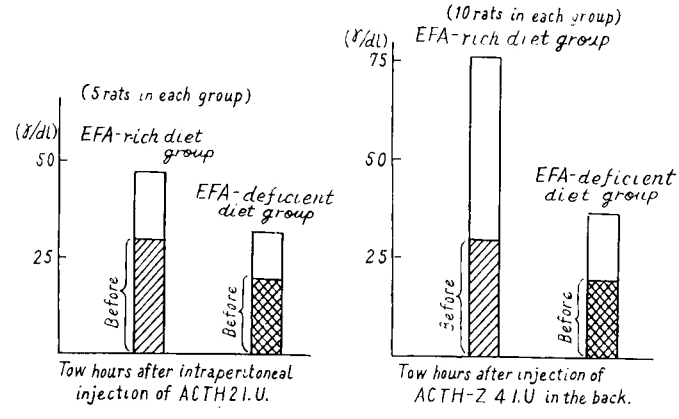


Fig. 13 Effect of ACTH on plasma fluorometric corticoids (rat).

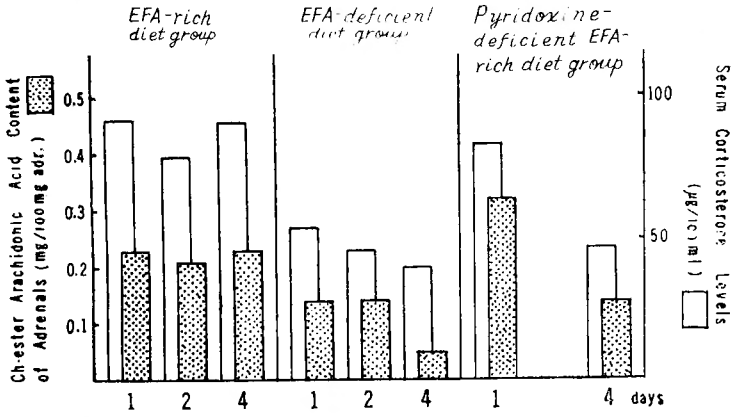
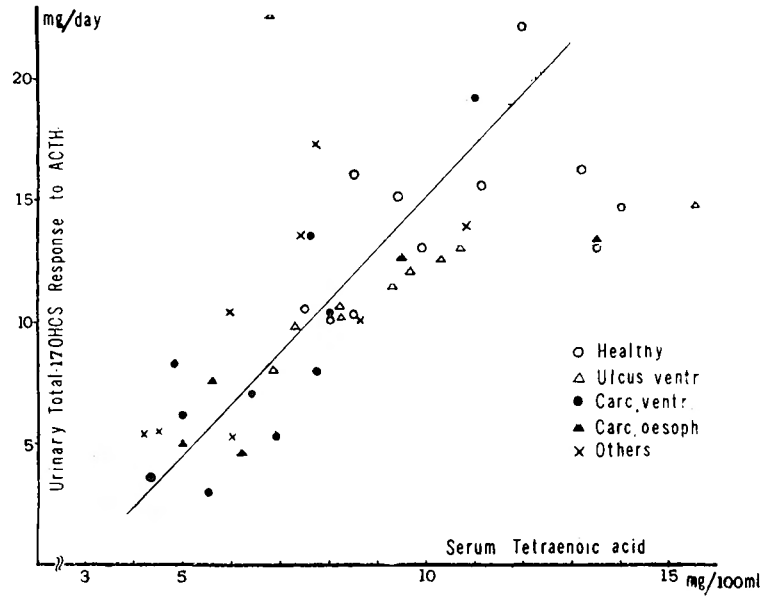


Fig. 14 Serum corticosterone levels and arachidonic acid content in adrenal cholesterol ester of the three diet groups during daily administration of ACTH-Z 3 I. U. for 4 days (rat).



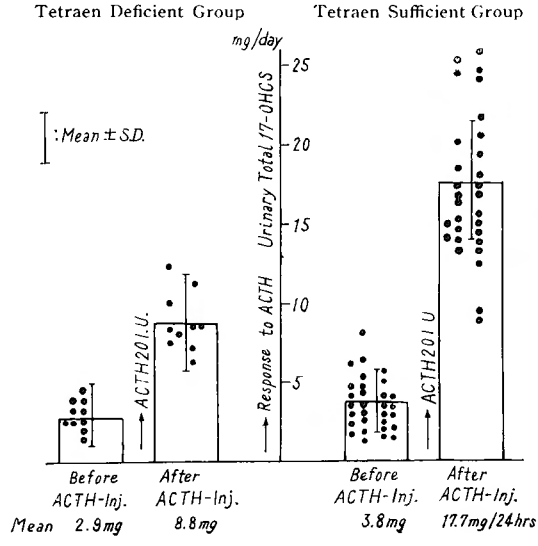


Fig. 15 The relationship between serum tetraenoic acid levels and total 17-OHCS response in urine in ACTH-test (surgical patients).

Since essential fatty acid deficiency may be associated with the disturbed metabolism of cholesterol which in turn leads to the inhibited synthesis of glucocorticoids in the adrenals, the adrenals of animals received an EFA-deficient diet cannot respond sufficiently to the increased hormonal demand of the organism when subjected to such stresses as infection, operative insult and trauma, and cannot suppress the abnormal increase of capillary permeability (Figs. 11～15, and Table 4).

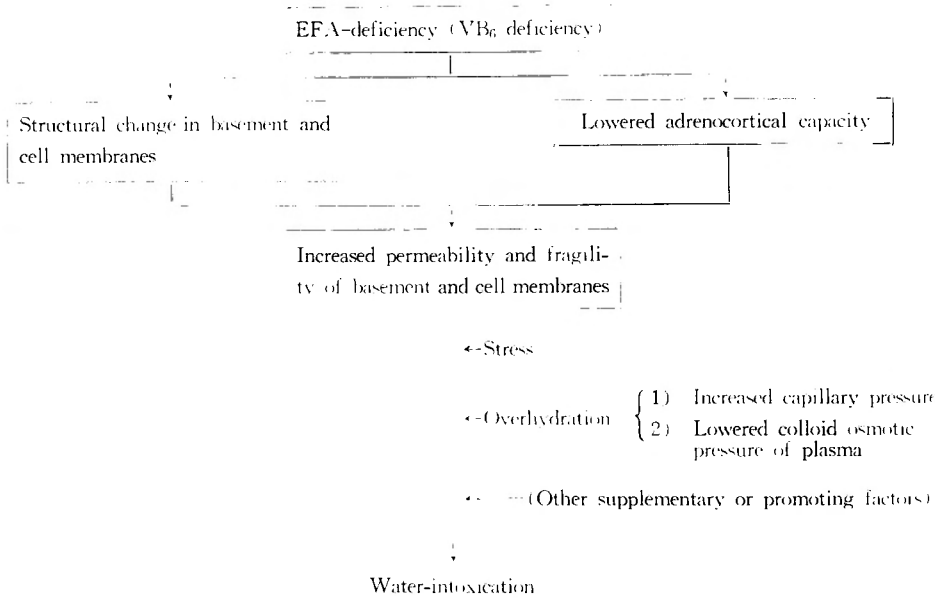
Table 4 Resting levels of plasma fluorometric corticoids (rat)

No.	EFA-rich diet group		EFA-deficient diet group	
	B. W.	γ/dl	B. W.	γ/dl
1	170g	21.2	285g	21.3
2	160	16.3	175	21.4
3	212	36.3	200	22.4
4	230	39.9	170	18.1
5	250	21.2	150	10.8
6	154	32.3	185	16.5
7	190	43.8	185	33.4
8	180	15.9	195	6.2
9	245	33.5	235	11.3
10	235	26.2	240	20.2

Mean 29.3±8.99γ/dl ・ Mean 18.5±7.30γ/dl

V. CONCLUSION

The reasons of the high incidence of water-intoxication in EFA deficient organisms could be summarized as follows.



And, in the EFA-deficient organism with disturbance in pulmonary circulation, water-intoxication develops easily in the form of APPE.

REFERENCES

1) Wakizaka, J.: Acute postoperative pulmonary edema, its pathogenesis and early diagnosis. Journal of the Japanese Association for Surgery, **61** : 885, 1960.
2) Wakizaka, J. et al.: Dangerousness of acute postoperative pulmonary edema and its prophylaxis and treatment. Nihon-Rinsho, **22** ・ 985, 1964.
3) Ishikawa, H.: Acute postoperative pulmonary edema, its prophylaxis and treatment. Journal of the Japanese Association for Surgery, **61** : 915, 1960.

4) Urabe, M : Acute postoperative pulmonary edema, its relationship with central nervous system. Ibid, **61** : 897, 1960.
5) Sakakibara, S. : Ibid, **61** : 919, 1960.
6) Yamaguchi, M . Electron microscopic study of experimental pulmonary edema. Archiv für Japanische Chirurgie, **29** · 482, 1960.
7) Chambers, R. et al. : Intercellular cement and capillary permeability. Physiological Reviews, **27** : 131, 1947.
8) Kramár, J. et al. : Influence of fats and fatty acids on the capillaries. Journal of Nutrition, **50** : 119, 1953.
9) Nagase, M. : Experimental study on pathogenesis of acute postoperative pulmonary edema. Archiv für Japanische Chirurgie, **29** : 67, 1960.
10) Nagase, M et al. : Lipids and adrenocortical function. Sushin-Igaku, **17** : 941, 1962.
11) Hikasa, Y. et al. : Role of adrenal lipids. Nihon-Rinsho, **22** : 112, 1964.
12) Hikasa, Y. et al. : Lipid metabolism in surgical field. Nihon-Rinsho, **22** · 509, 1964.
13) Hikasa, Y. et al. : Nutritional significance of lipids. Sogō-Igaku, **19** : 95, 1962.
14) Tamaki, Y. : Experimental study on the effect of essential fatty acid deficiency on adrenocortical function. Archiv für Japanische Chirurgie, **30** : 611, 1961.
15) Nakashio, S. : Experimental study on the essential fatty acids in organs. Ibid, **31** : 48, 1962.
16) Kobayashi, M : Studies on fluid metabolism in essential fatty acid deficiency. Ibid, **30** : 431, 1961.