Digestion and Absorption in Totally Depancreatized Dog, with Special Reference to the Influence of Estrogen on Digestion and Absorption of Fat

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CONTENT

I. INTRODUCTION

It has been known since early days that metabolism of fat is seriously influenced by the function of the pancreas. Lombroso asserted that the pancreas promotes fat metabolism, including absorption of fat, regardless of degenerative change of the organ[1]. With the marvellous advancement of pancreas surgery in recent years, propriety of total pancreatectomy became to be discussed. Early reports on the disturbances after total pancreatectomy were mostly concentrated on the occurrence of fatty liver. In 1890, von

The gist of the article was presented at 37th Meeting of Jap. Endocrinol. Soc., 43rd Meeting of Zyuzen-igakkai and 8th Meeting of Jap. Soc. of Diabetes.

MEHRING, MINKOWSKI and others reported lethal cases of fatty liver in dogs after total pancreatectomy[2]. Owing to the discovery of insulin by BANTING and BEST[3], FISCHER, ALLAN and others studied, in 1924, disturbances after total pancreatectomy under the administration of insulin and reported that occurrence of fatty liver cannot be prevented by the administration of insulin of any dosis[4][5]. MACLEOD reported, moreover, that occurrence of fatty liver can be well avoided by feeding totally depancreatized dogs with diet containing raw pancreas[6]. On the other hand, HARSHEY and others studied about anti-fatty liver action of lecithin and BEST, FERGUSON and others presumed this action of lecithin to be due to that of choline and thus they established fundamental concept of anti-fatty liver substance[7][8]. Concerning the anti-fatty liver factor in raw pancreas, BERG, ZUCKER and others presumed the existence of some hormone in pancreatic juice[9], and PROHASKA, DRAGSTEDT and others conceived some new hormone of the pancreas other than digestive enzymes or choline and named it *lipocaic*[10][11]. RALLI, CHAIKOFF and other disapproved of this assertion based on the fact that fatty liver as well occurs by the ligation of the pancreatic duct, and they reported that pancreatic juice similarly is possessed of anti-fatty liver action as well as extraction of the pancreatic tissue[12][13].

Since BERNARD investigated relationship between the pancreas and absorption of fat[14], in 1856, numerous studies have been made on digestion and absorption after total pancreatectomy, all of which pointed out serious disturbance of digestion and absorption, particularly, that of fat with resulting steatorrhea. According to reports of COFFEY[15], SELLE[16], HAMANO[17] and others, in addition, these data show some range of fluctuation and absorption rate of fat sometimes shows even negative equilibrium[17].

NISHIKAWA, in our clinic, reported recently that amount of feces was remarkably reduced, the tendency of steatorrhea also being imporoved, when gonadotropin or estrogen was simultaneously administered with insulin in totally depancreatized female dogs[18]. In these dogs, weight loss was also slighter than in those treated simply with insulin.

In the present experiment, influence of estrogen administration in totally depancreatized dogs on digestion and absorption was investigated by examining digestion and absorption with chrome oxide labelling method. Absorption test of ^{131}I-oleic acid for the study of fat metabolism and examination of hepatic bile were also carried out.

II. MATERIALS AND METHODS

A. Materials

Adult mongrel dogs weighing approximately 10 kg were used regardless of sex. Total pancreatectomy was constantly performed in all animals, which were divided into 4 groups postoperatively depending upon drugs administered and fed mainly with boiled rice and fishes. For the postoperative treatment, Isuzilin (Shimizu Pharm. Co. Ltd.) was used as insulin, and Estradio-Benzoate (Teikoku Zoki Co. Ltd.) as estrogen.

1. Group of Simple Administration of Insulin

One to two units per kg body weight of Isuzilin was administered successively everyday.

2. Group of Simple Administration of Estrogen

One thousand units per kg body weight of Estradiol-Benzoate was administered suc-

cessively everyday.

3. Group of Simultaneous Administration of Insulin and Estrogen

One to two units per kg body weight of Isuzilin and 1,000 units per kg body weight of Estradiol-Benzoate were successively administered everyday.

4. Group without Administration of Drugs

Neither insulin nor estrogen was administered in this group.

B. Methods

1. Production of Totally Depancreatized Dogs.

Animals were kept away from diet for 12 hours prior to surgery. As the premedication, 12.5 mg of Cacktelin H was intramuscularly injected 1 hour before surgery. The animals were anesthetized with intravenous injection of thiopenthal sodium of 15 to 30 mg per body weight from the femoral vein spending considerable time, and the operative procedure was carried out under adequate depth of anesthesia. The abdomen was opend with upper median incision, and the pancreas was freed from the surroundings, carefully isolating the pancreaticoduodenal artery and vein, their, branches to the duodenal side and the common bile duct, lest all these should be injured, and finally ligating and severing the vessels on the pancreatic side. Particular attention was paid to the isolation of the tissue around the main and accessory pancreatic ducts, since in this area the pancreatic tissue is tightly connected to the duodenal wall.

2. Examination of Digestion and Absorption by the Use of Chrome Oxide Labelling Method

Following the study of HONDA[19] in our clinic, dry bread with a uniform constitution was used. At the time of test, 200 g of this bread, 180 cc of milk and 300 cc of water were mixed together to become homogenous mixture and administered to the experimental animals (Tab. 1). During the period of the exmination, above mentioned mixture of examination food and water were exclusively administered. Material of feces was collected from more than 3 days after the commencement of the administration of examination food, a part of which was dried to powder and preserved. Analysis of protein in the material was performed by Azotometry[20], that of fat by method of van de KAMER A[21] and non-organic components by method of KONIG[22], and analysis of carbodydrate by the

Tab. 1 Examination Food

1)	Dried Bread			
	Flour	22.4 kg	Crude Fat	7.64%
	Powdered Milk	3.0	Crude Protein	12.39
	Lard	2.0	Crude Carbohydrate	77.38
	Sugar	2.0	Non-organic Components	2.59
	Salt	600.0 g	Chrome Oxide	0.21
	Chrome Oxide	40.0 g		
2)	Above Described Bread	200 g	Crude Fat	9.44%
	Milk	180cc	Crude Protein	13.54
	Water	ca 300cc	Crude Carbohydrate	74.03
			Non-organic Components	2.89
	to make homogenous mixture.		Chrome Oxide	0.18

differece from above mentioned components and that of chrome oxide by method of SCHURCH-DUNSKY-HILL[23)24)]. Absorption rate of each component was calculated from the following formula,

$$\text{Absorption rate } (\%) = \left(\frac{a-b}{a}\right) \times 100,$$

whereby a represents the proportion of each component in the examination food to chrome oxide and b represents the proportion of that component in the feces to chrome oxide. Total absorption rate was calculated from the following formula,

$$\text{Total absorption rate } (\%) = \left(1 - \frac{A}{a}\right) \times 100,$$

whereby A represents content of chrome oxide in the examination food (%) and a represents content of chrome oxide in the feces (%). This examination was carried out in animals of 3 groups of simple administration of insulin, simple administration of estrogen and simultaneous administration of insulin and estrogen, and the examination was carried out later than 4 weeks after surgery in groups of simple administration of insulin and simultaneous administration of insulin and estrogen, and later than 2 to 3 weeks after surgery in group of simple administration of estrogen.

3. Absorption Test of ^{131}I-Oleic Acid

Twenty-five μC of ^{131}I-oleic acid was added to 5 cc of olive oil, which was further emulsified with in 200 cc of water. Examination food was made from 100 g of above mentioned bread containing chrome oxide and the emulsion of ^{131}I-oleic acid. Saturation of the thyroid gland was carried out by Lugol solution on the previous day of surgery and the examination was done under the condition of 12 hours' fasting. At feeding of the examination food, attention was paid so that the animals might finish eating as soon as possible and the food might not be remained. After the feeding, the animals were kept away from food for 4 hours, and 2 cc of blood was taken every hour for 4 times from 3 hours after the feeding. Radioactivity of 1 cc of the blood was determined by well-type scintillation counter for 1 minute. On the other side, assuming circulating blood volume to be 7.5 per cent of body weight, radioactivity of circulating blood was calculated. Absorption rate of radioactivity in blood was obtained from the percentage of radioactivity in circulating blood to the entire radioactivity administered. Bowls used for the preparation and administration of examination food were adequately rinsed with BLOOR's reagent and radioactivity of the rinse solution was determined, which was then subtracted from the entire radioactivity added to the examination food and this result was assumed to be the radioactivity actually administered. Feces were collected 24 hours after the examination and well ground to powder, some part of which was put on a filter paper and its radioactivity was determined. This powder of feces was further put in a crucible and burnt to ash completely. Amount of chrome oxide contained in the ash was determined, and from the radioactivity and amount of chrome oxide in the material and amount of chrome oxide in the examination food, total radioactivity in the feces was obtained. Outlet rate in feces was represented in the term of percentage of radioactivity in feces to total radioactivity administered.

This examination was carried out in 2 groups of simple administration of insulin and simultaneous administration of insulin and estrogen, more than 4 weeks after the operation.

4. Studies on Character of Hepatic Bile

Collection of hepatic bile was done after 24 hours' fasting. Animals were anesthetized with interavenous injection of 3 to 5 mg of thiopethal sodium per kg body weight and the abdomen was opened with upper median incision. The cystic duct was first ligated and a small incision was laid on the common bile duct near the duodenum, from which a polyvinyl tube was inserted for the collection of hepatic bile. Prior to the collection of hepatic bile, bile collected during the initial 30 minutes was discarded in order to prevent mixing of cystic bile and the bile obtained later was assumed to be hepatic bile. Collection of bile was carried out 1 week after surgery in the group without administration of any drugs, and 4 week after surgery in other 3 groups. For the control study, similar study was done in 10 normal dogs. Following studies were carried out on the bile obtained.

i. Volume of Hepatic Bile

Volume of hepatic bile per hour per kg body weight was sought.

ii. Total Bile Acid

Total bile acid was determined as a sum of cholalic and desoxycholalic acids, as determined by MURAKAMI's method[25].

iii. Total Phospholipids

Fat phosphorus was determined by the method of FISKE-SUBBARAW[26], 25 times of which was taken as total phospholipids.

iv. Total Cholesterol

Total cholesterol was determined by modified method of ZAK KILLIANI[27].

5. Fluctuation of Body weight

Body weight was weighed before noon and before feeding once a week preoperatively and postoperatively for 4 weeks. Rate of weight loss was calculated from the following formula,

$$\text{Rate of weight loss} = \left(\frac{\text{Preoperative weight} - \text{Postoperative weight}}{\text{Preoperative weight}}\right)$$

Tab. 2 Crude Absorption Rate in Totally Depancreatized Dogs
Group of Simple Administration of Insulin (I)

		Fat	Protein	Carbohydrate	Total Absorption Rate
		(%)	(%)	(%)	(%)
I. 2	♂	12.8	29.6	52.7	44.5
I. 3	♀	43.6	28.3	76.4	50.3
I. 5	♂	36.7	24.3	71.3	48.1
I. 6	♀	23.1	17.4	68.9	43.6
Mean		29.1	24.9	67.3	49.1

III. RESULTS

A. Crude Absorption Rate by the Use of Chrome Oxide Labelling Method

1. Group of Simple Administration of Insulin

In the results of 4 dogs, absorption rate of fat was 29.1 per cent, on the average, although with considerable fluctuation of each datum. Absorption rate of protein was 24.9 per cent, on the average, similarly showing marked decrease as that of fat. Absorption rate of carbohydrate decreased less slightly compared with that of the former two, to be 67.3 per cent. Total absorption rate was remarkably reduced to be 49.1 per cent (Tab. 2).

Tab. 3 Crude Absorption Rate in Totally Depanoreatized Dogs
Group of Simple Administration of Estrogon (E)

		Fat	Protein	Carbo-hydrate	Total Absor-tion Rate
		(%)	(%)	(%)	(%)
E. 1	♂	42.2	23.7	72.9	62.2
E. 4	♂	37.5	18.2	68.2	43.2
E. 5	♂	45.8	26.9	76.3	46.8
E. 19	♀	19.6	19.4	64.3	39.5
E. 25	♂	23.2	21.5	75.4	46.2
Mean		33.7	21.9	71.4	47.6

Tab. 4 Crude Absorption Rate in Totally Depancreatized Dogs
Group of Simultaneous Administration of Insulin and Estrogen (C)

		Fat	Protem	Carbo-hydrate	Total Absorp-tion Rate
		(%)	(%)	(%)	(%)
C. 2	♂	83.8	36.0	77.9	73.5
C. 3	♂	81.5	35.6	91.7	81.9
C. 8	♀	88.7	34.7	85.6	87.0
C. 11	♂	76.4	29.7	79.3	76.1
C. 15	♀	80.3	35.4	82.8	80.3
Mean		82.1	31.0	83.5	79.8

2. Groug of Simple Administration of Estrogen

Average absorption rate of fat in 5 dogs was 33.7 per cent, and that of protein was 21.9 per cent, showing marked decrease, whereas decrease in absorption rate of carbohydrate was mild, the rate being 71.4 per cent, on the average. Total absorption rate showed as low a level as 47.6 per cent (Tab. 3).

3. Group of Simultaneous Administration of Insulin and Estrogen

Average absorption rate of fat in 5 dogs was 82.1 per cent, that of protein was 34.0 per cent and that of carbohydrate was 83.5 per cent, showing marked increase in absorption of fat and moderate increase in carbodydrate. Total absorption rate was 79.8 per cent (Tab. 4).

Summary

In both groups of simple administration of either insulin or estrogen, absorption rate remarkably decreased in fat and protein, while decrease in absorption rate of carbohydrate was relatively slight, showing similar tendency to each other. In contrast to these groups, absorption rate of fat was almost in normal level and that of carbohydrate and protein was also favorable in the group of simultaneous administration of insulin and estrogen. Total absorption rate, also, was in the highest level in group of simultaneous administration of insulin and estrogen, whereas it was low in groups of simple administration of either insulin or estrogen (Fig. 1, 2 and 3).

Fig. 1 Crude Absorption Rate of Carbohydrate

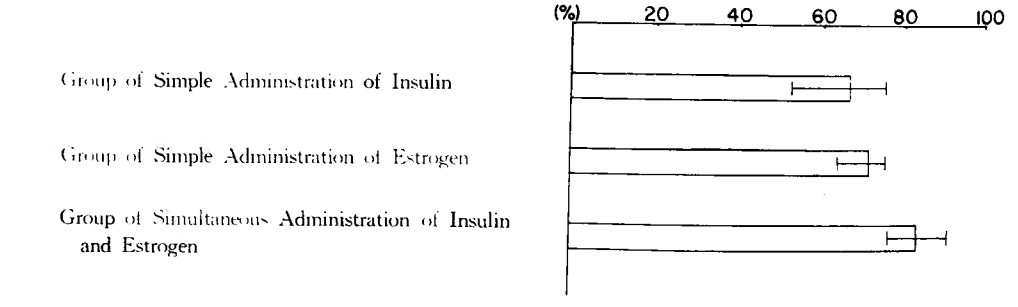


Fig. 2 Crude Absorption Rate of Fat

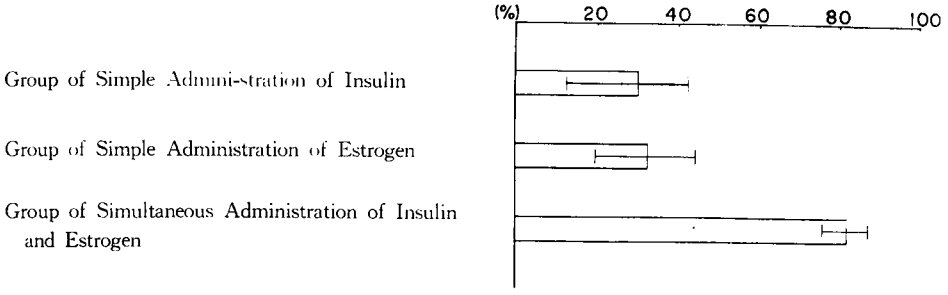
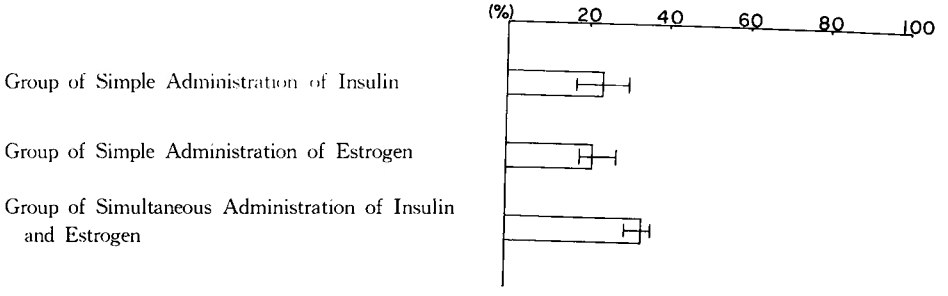


Fig. 3 Crude Absorption Rate of Protein



Tab. 5 Absorption Test of ^{131}I-Oleic Acid

		Absorption Rate in Blood				Absorption Rate in Feces
		3 hr	4 hr	5 hr	6 hr	
		(%)	(%)	(%)	(%)	(%)
C. 2	♂	5.54	9.07	7.91	7.81	9.6
C. 8	♀	3.49	3.86	4.13	4.23	12.7
C. 11	♂	3.06	2.83	2.34	2.77	10.1
Mean		4.03	5.26	4.79	4.94	10.8
I. 2	♂	0.21	0.34	0.43	0.50	23.6
I. 5	♂	0.21	0.38	0.26	0.23	28.6
I. 6	♀	0.35	0.22	0.46	0.49	27.1
Mean		0.27	0.31	0.35	0.41	26.5

C : Group of Simultaneous Administration of Insulin and Estrogen
I : Group of Simple Administration of Insulin

B. Absorption Test of ^{131}I-Oleic Acid

The maximum value of average absorption rate of ^{131}I-oleic acid in blood from 3 animal of group of simple administration of insulin was observed at 6th hour of the test to be 0.41 per cent and average out-let rate in feces was 26.5 per cent. On the other hand, in 3 animals of group of simultaneous administration of insulin and estregen, the maximum value of average absorption rate of ^{131}I-oleic acid in blood was 5.25 per cent at 4th hour of the test and out-let rate in feces was 10.8 per cent (Tab. 5).

Summary

From above mentioned results, it is assumed that both absorption rate in blood and out-let rate in feces of ^{131}I-oleic acid decreases remarkably in group of simple administration of insulin, whereas in group of simultaneous administration of insulin and estrogen these values showed nearly normal level.

C. Studies on Character of Hepatic Bile

1. Volume of Hepatic Bile

Average value of volume of hepatic bile in 10 normal dogs was 0.3 cc h kg body

Tab. 6 Constitution of Hepatic Bile in Normal Dogs (10 Cases)

Amount of Bile cc/h/kg	Bile Acid mg/h/kg	Phospholipids mg/h/kg	Total Cholesterol $\times 10^{-2}$mg/h/kg
Maximum / Minimum	Mean Value		
0.53 / 0.14 — 0.31	11.3 / 1.5 — 5.8	5.21 / 1.03 — 2.47	12.60 / 3.33 — 7.19

Tab. 7 Constitution of Hepatic Bile in Totally Depancreatized Dogs

	Amount cc/h/kg	Bile Acid mg/h/kg	Phospholipids mg/h/kg	Total Cholesterol $\times 10^{-2}$mg/h/kg
C. 31	0.11	1.3	1.74	5.32
C. 32	0.11	7.9	1.01	7.64
C. 33	0.20	15.1	1.10	15.80
Mean	0.14	9.1	1.28	9.25
I. 31	0.06	2.4	0.51	4.40
I. 32	0.13	5.8	1.17	6.92
I. 33	0.08	3.7	0.84	9.55
Mean	0.09	4.0	0.84	6.99
E. 31	0.08	2.6	0.35	4.42
E. 32	0.11	3.0	0.25	3.33
E. 33	0.04	2.4	0.62	6.19
Mean	0.08	2.7	0.41	4.65
F. 31	0.08	5.6	0.66	7.12
F. 32	0.11	2.6	0.29	3.95
F. 33	0.06	3.0	0.21	3.62
Mean	0.08	3.7	0.40	4.90

C : Group of Simultaneous Administration of Insulin and Estrogen
I : Group of Simple Administration of Insulin
E : Group of Simple Administration of Estrogen
F : Group without Administration of Drugs

weight, it was 0.14 cc/h/kg body weight in group of simultaneous administration of insulin and estrogen, 0.09 cc/h/kg body weight in group of simple administration of insulin, 0.08 cc/h/kg body weight in group of simple administration of estrogen and 0.08 cc/h/kg body weight in group without administration (Tab. 6 and 7).

2. Total Bile Acid

Average value of total bile acid was the highest in group of simultaneous administration of insulin and estrogen to be 9.1 mg/h/kg body weight, on the other hand it was 4.0 mg/h/kg body weight in group of simple administration of insulin, 2.7 mg/h/kg body weight in group of simple administration of estrogen and 3.7 mg/h/kg body weight in group without administration, revealing no marked difference among the latter 3 groups (Tab. 6 and 7).

3. Total Phospholipids

Average value of total phospholipids in normal dogs was 2.47 mg/h/kg body weight. It was 1.28 mg/h/kg body weight in group of simultaneous administration of insulin and estrogen, 0.84 mg/h/kg body weight in group of simple administration of insulin, 0.41 mg/h/kg body weight in group of simple administration of estrogen and 0.40 mg/h/kg body weight in group without administration. The value was the most near the normal one in group of simultaneous administration of insulin and estrogen (Tab. 6 and 7).

4. Total Cholesterol

Average value of total cholesterol in normal dogs was 7.49×10^{-2} mg/h/kg body weight, and totally depancreatized dogs showed no difference of the value from normal one. It was 9.25×10^{-2} mg/h/kg body weight in group of simultaneous administration of insulin and estrogen, 6.99×10^{-2} mg/h/kg body weight in group of simple administration of insulin, 4.65×10^{-2} mg/h/kg body weight in group of simple administration of estrogen and 4.90×10^{-2} mg/h/kg body weight in group without administration (Tab. 6 and 7).

Summary

These results reveal that there is no significant difference between normal dogs and totally depancreatized dogs as far as total bile acid and total cholesterol are concerned, and there could not be observed any marked difference among each of group of totally depancreatized dog. However, hepatic bile and total phospholipids showed considerably low level in totally depancreatized dogs compared with normal ones. Among 4 groups of totally depancreatized dogs, group of simultaneous administration of insulin and estrogen showed the levels the most near the normal ones.

D. Fluctuation of Body Weight (Weight Loss Rate)

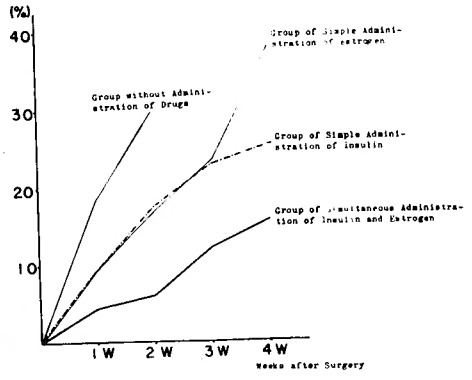
A week after surgery, weight loss rate in group of simultaneous administration of insulin and estrogen was 4.4 per cent, 9.5 per cent in group of simple administration of insulin, 9.3 per cent in group of simple administration of estrogen and 18.3 per cent in group without administration. Weight loss was particularly remarkable in group without administration. Two week after surgery, weight loss rate was 6.2 per cent in group of simultaneous administration of insulin and estrogen, 17.4 per cent in group of simple administration of insulin, 17.0 per cent in group of simple administration of estrogen and 30.1 per cent in group without administration, revealing outstandingly slight decrease in group of simultaneous administration of insulin and estrogen and remarkably pronounced decrease in group without administration, the latter soon expiring from fatty liver. Three weeks after surgery, weight loss rate was 12.1 per cent is group of simultaneous administration of insulin and estrogen, showing a low level as ever, 23.1 per cent in group of simple administration of insulin and 23.6 per cent in group of simple administration of estrogen, the latter two showing a similar tendency. For weeks after surgery, weight loss rate was 15.7 per cent in group of simultaneous administration of insulin and estrogen, 25.5 per cent in group of simple administration of insulin and 37.9 per cent in group of simple administration of estrogen. Weight loss was marked in group of simple administration of estrogen and the animals soon died from debility (Tab. 8).

Tab. 8 Weight Loss Rate in Totally Depancreatized Dogs

	After Surgery (Weeks)			
	1	2	3	4
Group without Administration of Drugs	14.3 / 18.8 18.3 (5)	28.6 / 31.3 30.1 (3)		
Group of Simple Administration of Estrogen	4.8 / 13.8 9.3 (10)	6.7 / 31.0 17.0 (10)	13.6 / 35.7 23.6 (10)	36.8 / 39.3 37.9 (5)
Group of Simple Administration of Insulin	1.9 / 12.5 9.5 (6)	11.8 / 21.1 17.4 (6)	16.0 / 29.2 23.1 (6)	23.5 / 33.7 25.5 (6)
Group of Simultaneous Administration of Insulin and Estrogen	0 / 6.7 4.4 (9)	5.6 / 8.0 6.2 (9)	5.6 / 25.0 12.1 (9)	8.0 / 25.0 15.7 (8)

Minimum (%) / Maximum (%) ~ Mean Value (%) (Number of Dogs)

Fig. 4 Weight Loss Rate in Totally Depancreatized Dogs



Summary

Although weight loss was observed in all groups of totally depancreatized dogs, it was particularly marked in group without administration. On the other hand, weight loss in group of simple administration of estrogen showed roughly similar tendency of decrease to group of simple administration of insulin until 3rd week after surgery, but the former showed rapid debility to death around 4th week after surgery. Rate of weight loss was slight in group of simultaneous administration of insulin and estrogen (Fig. 4).

IV. DISCUSSION

There are reports of COFFEY[15], SELLE[16], HAMANO[17], EGAWA[18] and other on digestion and absorption after total pancreatectomy. All of these deal with the problems of absorption under the administration of either insulin or anti-fatty liver substance. What is common to all these reports in that disturbance of digestion and absorption of carbohydrate is relatively mild and that of fat and protein is seriously profound. Concerning absorption of fat, particularly, it is reported that the datum varies largely and sometimes it shows negative equilibrium[27]. In this respect, IWATSURU explained that absorption rate of fat increases by increasing the intake of fat, presuming from the relationship between the amount of endogenous fat and that of fat contained in food[29]. This was agreed by WOLLAEGER and others[30]. KOSAKI also reported that endogenous fat increased to more than 2 g[31].

In the present experiment, in order to avoid fluctuation of data caused by endogenous fat, the amount of examination food was determined to be constant and common method of feeding as approximately 80 Cal/kg body whight, which is based on body weight, was not adopted. However, there was little difference in the results of group of simple administration of insulin when compared with the results as have been reported, in addition fluctuating in a considerable range. Accordingly, it is assumed that variety of the results of fat absorption rate in totally depancreatized dogs is largely dependent on the general condition of individual dogs.

As the cause of particular decrease in fat absorption rate after total pancreatectomy, digestive disturbance due to lack of pancreatic lipase can be first considered, but it has been said that above mentioned decrease in fat absorption rate connot be adequately explained solely by this and some other important factors can possibly exist. For instance, VERMEULEN and others maintained, from the fact of disturbance of absorption of oleic acid after total pancreatectomy, that there obviously exist some abnormality in the process of absorption[32]. HAMANO reported that absorption rate in totally depancreatized dogs (with resection of the duodenum) was 16.18 per cent and that in dogs with ligation of the pancreatic duct (with resection of the duodenum) was 57.0 per cent, revealing marked

difference, and from this finding, he considered this difference observed between 2 groups of animals assumed identical in the respect of absence of pancreatic juice is duo to disturbance of absorption[17]. Thus, he further suggested existence of unknown endocrine mechanism of the pancreas participating in the absorption of fat. Results of ^{131}I-oleic acid absorption test in group of simple administration of insulin in the present experiment are accepted to domonstrate the disturbance of absorption, corresponding to the results of EGAWA[28]. According to 'particulate absorption theory', absorption process of fat in normal condition is generally considered to be achieved by absorption in the epithelial cells in a form of fat droplets smaller than 0.5 μ in diameter[33]. PALAY, Karlin and others have clarified from electrone microscopic studies that fat droplets are taken into the epithelial cells in a form of 'pinocytosis'[34]. However, there are not a few assertions contradicting this pinocytosis theory[35][36]. Any way, fat taken into the intestinal epithelial cells is once hydrolysed[40] by the enzymes[37][38][39] in the epithelial cells. Fatty acid produced at this hydrolysis and taken from the intestinal canal in a form of fatty acid are conveyed to metabolic process of 2 types depending upon their length of carbonic chain. Most of molecules of fatty acid having carbonic chain of 10 or less are conveyed to the portal vein in non-esterified form[41][42][43], and fatty acid having longer carbonic chain of 10 to 12 or more is synthetized again to triglycerid[43][44] and appears in the lymph of the thoracic duct in a form of chylomicron[41][43]. Glycerol for to-be-resynthetized triglyceride comes very little from diet[45] and most of it is from endogenous glycerol derived from L-α-glycerophosphoric acid produced by glycolysis[46]. Triglyceride never changes by itself into chylomicron, which appears in the lymph. In order to become stable emulsion as chylomicron, certain detergent, and judging from the chemical construction of chylomicron[47], lipoprotein composed from phospholipid and protein is considered to play the role of detergent in this occasion[36]. Accordingly, formation of chylomicron is accomplished by synthesis of lipoprotein, which proceeds in parallel with resynthesis of triglyceride in the intestinal epithelial cells. This is the summarized absorption mechanism of fat in normal condition. In what part of this absorption process does the disturbance occur after total pancreatectomy? Concerning this point, FERNANDES, van de KAMER and others pointed out that absorption of lower fatty acid having carbonic chain of less than 10 was not disturbed and absorption of only higher fatty acid was disturbed in patients of cystic fibrosis of the pancreas with steatorrhea[48], and they emphasized the interesting point of this problem, though this was not the cases of total pancreatectomy. In the histological studies of jejunal membrane of totally depancreatized dogs, EGAWA observed decrease in activity of alkaline phosphatase, succinic dehydrogenase and ATP-ase, and he presumed that the decrease in activity of these enzymes is closely related to shortage of energy at absorption of fat and disturbance of synthesis of fat in the membrane of epithelial cells[28]. SALT also pointed out disturbance of chylomicron formation as a cause of steatorrhea and related it to disturbance of lipoprotein metabolism[49]. From these observations, it is assumed that disturbance of fat absorption after total pancreatectomy consists in the disturbance of triglyceride resynthesis and formation of chylomicron.

In the present experiment, function of digestion and absorption was generally improved after total pancreatectomy by simultaneous administration of insulin and estrogen, absorp-

tion rate of fat, particularly, showing as high a level as 82.1 per cent in group of simultaneous administration of insulin and estrogen, compared with groups of either insulin with 29.1 per cent or estrogen with 33.7 per cent. Absorption rate of ^{131}I-oleic acid was also nearly in the normal level in group of simultaneous administration of insulin and estrogen. This fact is accepted to clarify that insulin and estrogen participate and give favorable influence in the disturbed absorption process of fat after total pancreatectomy in dogs. Concerning the significance of insulin in absorption process, energy supply and supply of active glycerol at resynthesis of triglyceride can be considered. As to estrogen, it is assumed that estrogen promotes utilization and transport of fat through phospholipids, and consequently it influences on triglyceride synthesis and formation of chylomicron. HOUSSAY observed an improvement of diabetes mellitus by the administration of estrogen in subtotally depancreatized rats, and he explained that estrogen promotes proliferation of islet cell with resulting increase in insulin[50]. However, from the findings of the present experiment, some independent action of estrogen can be admitted besides the action of insulin. TANIGUCHI, in our clinic, pointed out rare occurrence of fatty liver after pancreatectomy in the similar experimental dogs as in the present experiment, particularly in dogs with simple administration of estrogen, and he presumed that estrogen might have influenced favorably in the improvement of phospholipids metabolism[51]. Considering from the resemblance of secretion of triglyceride in the liver[52] and formation of chylomicron in the intestine and the importance of phospholipids participating in these processes, it is assumed that improvement of fat absorption and prevention of fatty liver are both attributable to favorable influence of estrogen on phospholipids metabolism.

On the other hand, concerning character of hepatic bile in totally depancreatized dogs it was anticipated that digestion and absorption of fat would be influenced by the alteration of bile acid metabolism due to lipid shifting action of estrogen[53], but little change was observed in total bile acid and decrease in phospholipids, generally considered to occupy most part of bile lipids, was noticed. In addition, it is interesting, when considered together with above mentioned action of estrogen, that simultaneous administration of insulin and estrogen improved the decrease in phospholipids. Furthermore, although weight loss after total pancreatectomy has been considered to be inevitable, it could be favorably avoided within the slightest decrease by the simultaneous administration of estrogen.

V. SUMMARY

1. Simultaneous abministration of insulin and estrogen improved whole mechanism of digestion and absorption, particularly digestion and absorption rate of fat being 29.1 per cent in group of simple administration of insulin and 33.7 per cent in group of simple administration of estrogen, whereas it being markedly favorable to be 82.1 per cent in group of simultaneous administration of insulin and estrogen.

2. ^{131}I-oleic acid absorption test reached the maximum of 5.25 per cent 4 hour after the feeding of examination food as determined by absorption rate in blood in group of simultaneous administration of insulin and estrogen with out-let rate in feces in the level of 10.8 per cent, both of which being near the normal level, while in group of simple administration of insulin, absorption rate in blood at 6th hour of the test was 0.41 per

cent and out-let rate in feces was 26.5 per cent, revealing serious disturbance of absorption.

3. Concerning the charactor of hepatic bile, decrease in hepatic bile could be observed in dogs of total pancreatectomy, with marked decrease in phospholipids. Simultaneous administration of insulin and estrogen improved this tendency of decrease.

4. Weight loss was commonly observed in each group of totally depancreatized dogs, particularly being pronounced in group with administration of neither insulin nor estrogen to be 30.1 per cent 2 weeks after surgery. On the contrary, in group of simultaneous administration of insulin and estrogen, weight loss was only 15.7 per cent as late as 4 weeks after surgery, showing slighter decrease compared with other 3 groups. Weight loss in groups of simple administration of either insulin or estrogen showed similar tendency to each other, although animals in the latter group swiftly driven to dibility and succumbed to death.

As observed and discussed in the present paper, it is assumed that estrogen has a favorable influence on digestion and absorption of totally depancreatized dogs.

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和文抄録

膵全剔犬に於ける消化吸収機能，特に脂肪の消化吸収機能に及ぼすエストロゲンの影響について

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深　谷　桂　一

膵全剔後の主なる病態は糖尿病，脂肪肝及び消化吸収障害であるが，このうち糖尿病と脂肪肝は適量のインシュリン投与により，かなりの障害軽減をはかることが可能である．しかし，消化吸収障害は膵外分泌機能廃絶が根底にあるだけに，インシュリンのみの投与による改善は望むべくもない．事実諸家の報告でもインシュリン投与の膵全剔犬に於ける消化吸収障害は著しく，殊に脂肪及び蛋白にその傾向が強く，炭水化物の吸収低下は比較的軽度とされている．

しかるに，最近教室の西川はインシュリン投与全剔犬にゴナドトロピン又はエストロゲンを併用すると糞便量が少く，Steatorrhoe の傾向も軽減し，体重減少もインシュリンのみの投与に比し目立つて少いことを報告している．著者はかかるエストロゲン投与が膵全剔犬の消化吸収機能に如何なる影響を与えているかを検討し次の結果を得た．

1. Cr_2, O_3 を指標物質とした消化吸収試験の結果によれば，膵全剔後，インシュリン・エストロゲンの併用は消化吸収機能を全般的に改善し，特に脂肪の消化吸収率はインシュリン単独投与群29.1%，エストロゲン単独投与群33.7%に比し82.1%と著しく好転した．

2. ^{131}I オレイン酸吸収試験もインシュリン・エストロゲン併用群では血中吸収率の最大値は4時間値5.25%，糞便排泄率10.8%と正常に近い値を示し，これに対しインシュリン単独投与群では血中吸収率6時間値が0.41%，糞便排泄率26.5%と著明な吸収障害を示した．

3. 肝胆汁成分については，膵全剔犬で胆汁量の減少が認められ，また燐脂質の減少が著しく，インシュリン・エストロゲンの併用はこの傾向を改善し正常値に近い値を示した．

4. 体重減少は膵全剔犬各群に共通して認められるが，特に無投与群では2週目にすでに30.1%の減少率を示した．一方インシュリンエストロゲン併用群では4週目においても15.7%の減少率があり，他3群に比し低値を示した．インシュリン単独投与群，エストロゲン単独投与群は類似の傾向を示すが，後者は4週に到り急に衰弱し後死亡する．