STUDIES ON FAT METABOLISM AFTER TOTAL PANCREATECTOMY. EXPERIMENTS IN DOGS.

by

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Fat metabolism, particulary in such a pathologic state as after total pancreatectomy, poses a very difficult problem. Fat, carbohydrate and protein do not metabolize individually and separately and are closely related with each other in vivo. As abnormality of carbohydrate metabolism reveals itself after total pancreatectomy, it may reasonably be assumed that fat metabolism comes to be deranged at the same time. Moreover, it has been recognized that the process of fat metabolism after total pancreatectomy differs from that after subtotal pancreatectomy or in diabetes mellitus (medical), despite the fact that hyperglycemia takes places equally in all these conditions.

In 1924 FISHER, ALLAN and others reported that completely depancreatized dogs usually failed to survive for a long period, even if treated adequately with insulin, and that a marked accumulation of fat in the liver was found to be the most prominent change in these dogs at autopsy.

Later, MACLEOD and others reported that feeding raw pancreas was effective in preventing the development of fatty liver which used to appear in depancreatized dogs. HERSHEY et al. found that daily administration of 10g "lecithin" to these animals prevented the occurrence of fatty liver as well.

In 1934, ENTENMAN, CHAIKOFF, and KAPLAN reported that totally depancreatized dogs showed hypolipemia, which was induced not by chronic inanition but by the development of fatty liver.

In 1936 DRAGSTEDT et al. expressed the opinion that the effect of oral administration of raw pancreas in preventing fatty liver might be accounted for by its content not of pancreatic enzymes or of choline, but of a specific substance which was believed by them to be a new hormone, named "lipocaic". They also stated that the pancreas played some role in the absorption of fat other than through the digestive action of pancreatic lipase.

Opposing DRAGSTEDT's theory, AOKI in our clinic reported that in almost all dogs which survived for a comparatively long period after total pancreatectomy without receiving raw pancreas, fatty liver did not usually occur.

Since ROCKEY (1943) first performed total pancreatectomy on man for pancreatic cancer, PRIESTLY, BRUNSCHWIG, DIXON and others successfully carried out this operation for malignant tumor or chronic inflammation of the pancreas, and not a few of these patients survived for a long period postoperatively. None of these patients presented signs of fatty liver during life; moreover, the fatty liver which was confirmed at autopsy in only one case was ascribed to diabetic coma (BRUNSCHWIG).

In our clinic, total pancreato-duodenectomy was successfully performed on 8 cases including 1 case who is living a healthy life now, 4 years after the operation. In this series of our patients, fatty liver was recognized in only one case at autopsy 5 months after the operation who was proved to have generalized tuberculosis at the same time.

In 1953, HAMANO in our clinic reported that totally depancreatized men showed a higher absorption rate of nutriments than similarly treated dogs and the cause of the development of fatty liver after total pancreatectomy appears to be the lowering of the absorption rate of nutriments, especially of protein. Hence, fatty liver of this sort may belong to the category of alimentary fatty liver.

What changes of fat metabolism may occur after total pancreatectomy ?

In 1950, LOMBROSIO & DACHÁ reported an interesting observation that the depancreatized dogs eliminated 56.5 to 111.8 per cent of the fat in an olive oil emulsion given intravenously, while normal dogs tolerated the fat well and did not show steatorrhea, and presumed that the pancreas played some role in the intermediary fat metabolism.

It is well known that ketosis is apt to occur in severe clinical diabetes. Consequently it would seem probable that ketosis might readily appear after total pancreatectomy. However, FALLIS and KAWAMURA stated that in totally pancreatectomized patients ketosis did not occur as promptly as was expected. FRIEDMAN and DYE reported that ketone bodies were utilized in the extrahepatic tissues, despite removal of the pancreas.

According to these facts, it seems likely that fat metabolism may also be disturbed after total pancreatectomy by some factors other than total loss of pancreatic juice and hyperglycemia.

I wish to report here the data of my study on fat metabolism in depancreatized dogs given intravenous or oral fat emulsion.

MATERIALS

Adult dogs of about 10 kg of body weight were used, after having been fed a definite diet for more than a week.

Both totally pancreato-duodenectomized and totally pancreatectomized dogs were subjected to the present experiments. When necrosis of the duodenal wall is expected to occur after removal of the pancreas, because the pancreas is anatomically so closely related to the duodenum in dogs as well as in human beings, duodenectomy, gastro-jejunostomy and choledocho-jejunostomy were carried out subsequently. Dogs with subtotally resected pancreas and those with ligated pancreatic ducts were also studied for the sake of comparison.

These dogs were fed boiled rice, and barley together with dried fish. Pancreatin, methionin and V.B_1 were also administered in some cases.

Totally and subtotally pancreatectomized dogs were subcutaneously injected with insulin in such an amount that the blood suger level was kept constant at about 200 mg per 100 cc.

Fat Emulsion.

In the present experiments, a cod liver or sesame oil emulsion produced in the 2nd Surgical Division, Kyoto University, was used. This fat emulsion consists of fine fat globules less than 2μ in diameter. Neutral fat accounts for 85.5 per cent of the total fat (Table 1).

Table 1 Composition of Cod Liver Oil Emulsion

Neutral Fat	Fatty Acid	Lecithin
85.5%	7.9%	6.4%

The Diameter of Fat Globule (Cod Liver Oil)

2.0～0.8μ	under 0.8μ
30.4%	69.6%

METHOD OF MEASUREMENT AND HISTOLOGICAL STAINING

(A) Quantitative Determination of Total Fat.

Dried feces 1g, serum 1cc, chyle 1cc, and perfused fluid 1cc were examined. The amount of fat was determined by the method of VAN DE KAMER A.

(B) Quantitative Determination of Total Ketone Bodies.

Blood and perfused fluid 0.2cc, each, were examined. The level of total ketone bodies (expressed as acetone) was measured by the method of GREENEERG and LESTER.

(C) Staining of the Fat in the Liver.

Sudan III stain was applied to carbowax sections.

EXPERIMENTS AND RESULTS

(I) PROBLEMS CONCERNING THE DIGESTIVE ABSORPTIVE FUNCTION OF FAT AFTER TOTAL PANCREATECTOMY

Because of the total deficiency of pancreatic lipase, it is no wonder that the digestion-absorption rate of fat decreases considerably after total pancreatectomy. But we are deeply impressed by the fact that the rate is much lower in depancreatized dogs than in pancreatic-duct-ligated ones, as reported by HAMANO in our clinic, although the condition is the same in both groups in regard to the deficiency of pancreatic juice.

Some authors have remarked that in depancreatized men and dogs the digestion-absorption rate of fat is not only lowered but also fluctuates widely from case to case.

HAMANO also observed in depancreatized dogs that the absorption rate of fat fluctuated in such a wide range as -36.79% to $+55.56\%$, and in the worst cases the amount of the excreted fat in the feces exceeded that of the ingested fat. IWATSURU reported that the more the amount of ingested fat increased, the more the absorption rate of fat increased.

On the other hand, DRAGSTEDT considered that the decided impairment in the absorption of fatty acid after total pancreatectomy was somewhat surprising and might indicate that the pancreas played some role in the absorption of fat other than through the digestive action of pancreatic lipase.

(A) *Amount of Endogenous Fat in Feces.*

For a week a test diet containing only 0.4g of fat per day (Table 2) was given to the dogs and then all the feces excreted during the next 3 days were collected with charcoal as a marker, and the amount of excreted fat in the feces was determined' (Table 3).

Table 2 Test Diet (daily)

		Ca.	Totol Lipid
Polished Rice	100g	350	0.4g
Casein	50g	300	
Sugar	50g	190	
Soy	20cc	12	
Salt	1g		
Bulkose	1g		
		852	0.4

In depancreatized dogs taking the test diet the average amount of fat in the feces was 2.729g per day, whereas in pancreatic-duct-ligated dogs it was 1.185g and in normal dogs 0.597g. The amount of fat excreted in the feces of the depancreatized dogs exceeded by over 2g that of the normal dogs. In other words, it may be said that the amount of endogenous fat excreted in the feces increased markedly after total pancreatectomy.

Table 3 The Amounts of Endogenous Fat Excreted in the Feces

	Normal Dogs	Totally Depancreatized Dogs	Pancreatic Duct Ligated Dogs
The Amount of Endogenous Fat Excreted in the Feces (g)	0.547	2.859	1.254
	0.571	2.863	1.016
	0.674	2.952	
		2.424	
		3.040	
		2.568	
		2.399	
Average	0.597	2.729±0.61	1.185

(B) *Digestion-Absorption Rate after Total Pancreatectomy.*

It was ascertained that endogenous fat increased more than 2g after total pancreatectomy. Then, if one assumes that this amount of endogenous fat is excreted also when the fat-containing diet is given, one should subtract the amount of endogenous fat from the total amount of fat excreted in the feces, in order to obtain the more accurate absorption rate of fat after total pancreatectomy. Thus:

ordinary absorption rate of fat=

$$(\text{the ingested fat} - \text{the excreted fat in the feces}) \times \frac{100}{\text{the ingested fat}}$$

corrected absorption rate of fat={the ingested fat− (the excreted

$$\text{fat in the feces} - \text{the endogenous fat})\} \times \frac{100}{\text{the ingested fat.}}$$

First, the amount of endogenous fat in the feces of the depancreatized dogs fed the fatless test diet was determined, and then diets containing 3, 6, 13 5 or 18g of fat were administered and the feces collected for 3 days. The amount of fecal fat excreted per day was determined. From these results, both the ordinary absorption rate and corrected rate were calculated (Table 4).

Table 4 The Absorption Rate of Fat in Totally Depancreatized Dogs

	Case No.	Days after Operation	Fat in Diet Daily (g)	Fat in Feces Daily (g)	Ordinary Absorption Rate of Fat (%)	Corrected Absorption Rate of Fat (%)
Totally Depancreatized Dogs	1	55 – 70		2.568		
	2		3.0	3.391	−13.03	72.57
	3		6.0	4.557	24.05	66.85
	4		13.5	6.947	48.54	67.56
	5	6 – 21		2.399		
	6		3.0	3.523	−17.43	62.53
	7		6.0	8.678	38.70	78.68
	8		18.0	8.431	53.16	66.49
Pancreatic Duct Ligated Dogs	9	7 – 22		1.016		
	10		3.0	0.943	68.57	(100.00)
	11		6.0	1.316	78.07	95.00
	12		18.0	2.888	83.95	89.59

In depancreatized dogs, the ordinary absorption rate of fat fluctuated widely within a range of −17.43% to +53.16% but the corrected absorption rate of fat showed relatively constant values, +62.53 to +72.57% regardless of the amount of fat ingested. Especially when the diet containing 3g of fat was given, the corrected absorption rate of fat was over 60%, whereas the ordinary absorption rate of fat gave a negative percentage.

It is assumed that the ordinary absorption rate of fat usually fluctuated over a wide range because one did not take the existence of endogenous fat into consideration.

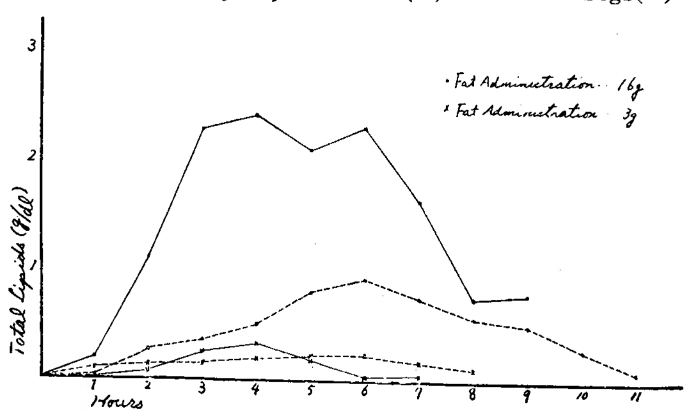
(C) *Absorption of Fat through the Thoracic Duct in Depancreatized Dogs.*

I tried to determine how much of the ingested fat could be absorbed through the thoracic duct in totally depancreatized dogs, although the corrected Digestion-absorption rate of fat suggested that more than 60% of ingested fat could be absorbed in the depancreatized dogs which was given 3g of fat per day orally.

Under isomythal anesthesia, a fistula of the thoracic duct was constructed as follows ;

a 5 cm long incision was

Fig. 1 Curves Showing Increments of Averaged Amounts of the Total Lipids in Chyle Following Oral Administration of Fat Emulsion in Totally Depancreatized(---) and Nomal Dogs(—)



made in the left supraclavicular fossa and the thoracic duct was isolated from the surrounding tissues, and then a polyethylene tube was inserted into the ampulla of the thoracic duct.

The chyle was collected at 1 hour intervals for 10 hours after the administration of fat via stomach tube. The concentration of fat in the chyle was determined (Table 5, Fig. 1).

In normal dogs, following oral administration of 16g of fat, the concentration of fat in the chyle showed a rapid increase of about 3g per dl. during the first 2 or 3 hours after the administration of fat and began to return to the preadministration level after 8 to 9 hours.

In depancreatized dogs, the concentration of fat in the chyle showed only an increase of 0.8 to 1.2g per dl. 4 or 6 hours after administration and began to return to the preadministration level thereafter.

Following the administration of 3g of fat, the change in fat concentration in the chyle showed no noticeable difference between normal dogs and depancreatized ones, and the increment of fat concentration was 0.3 to 0.5g per dl. 3 to 4 hours after the administration in both groups.

From these results, it is confirmed definitely that the depancreatized dogs are capable of absorbing fat from the intestine through the thoracic duct, even though the amount of fat absor-

Table 5 The Total Lipid Levels in Chyle Following Oral Administration of Fat Emulsion in Totally Depancreatized and Normal Dogs.

	Fat Given Orally (g)	Time	Before Adminis-tration	After Administration (Hours) 1	2	3	4	5	6	7	8	9	10	11
Totally Depancreatized Dogs	3.0	Total Lipids (Increment)	0.40 g/dl.	0.58 (+0.18)	0.66 (+0.26)	0.59 (+0.19)	0.58 (+0.18)	0.63 (+0.23)	0.62 (+0.22)	0.60 (+0.20)	0.53 (+0.13)			
	3.0	T. L. (I.)	0.37	0.38 (+0.01)	0.40 (+0.03)	0.46 (+0.09)	0.56 (+0.19)	0.56 (+0.19)	0.60 (+0.23)	0.53 (+0.16)	0.46 (+0.09)			
	16.0	T. L. (I.)	0.58	0.61 (+0.03)	0.66 (+0.08)	0.75 (+0.17)	0.92 (+0.34)	1.56 (+0.98)	1.80 (+1.22)	1.44 (+0.86)	1.22 (+0.64)	1.24 (+0.66)	1.00 (+0.42)	0.78 (+0.20)
	16.0	T. L. (I.)	0.83	0.87 (+0.04)	1.27 (+0.44)	1.36 (+0.53)	1.50 (+0.67)	1.46 (+0.63)	1.44 (+0.61)	1.46 (+0.63)	1.33 (+0.56)	1.17 (+0.34)	0.97 (+0.14)	0.93 (+0.10)
Normal Dogs	3.0	T. L. (I.)	0.39	0.37 (−0.02)	0.41 (+0.02)	0.47 (+0.08)	0.74 (+0.35)	0.60 (+0.21)	0.37 (−0.02)					
	3.0	T. L. (I.)	0.50	0.51 (+0.01)	0.65 (+0.15)	0.92 (+0.42)	0.79 (+0.29)	0.63 (+0.13)	0.56 (+0.06)	0.54 (+0.04)				
	16.0	T. L. (I.)	0.60	0.70 (+0.10)	1.10 (+0.50)	2.66 (+2.06)	2.32 (+1.72)	2.65 (+2.05)	3.51 (+2.91)	2.99 (+2.39)				
	16.0	T. L. (I.)	0.61	0.90 (+0.29)	2.33 (+1.72)	3.07 (+2.46)	3.69 (+3.08)	2.77 (+2.16)	2.36 (+1.75)	1.46 (+0.85)	1.36 (+0.75)	1.38 (+0.77)		

bed is reduced.

(II) DESTINY OF FAT ADMINISTERED INTRAVENOUSLY AFTER TOTAL PANCREATECTOMY

In order to determine whether abnormal signs of fat metabolism after total pancreatectomy, such as STAUB's effect in diabetes mellitus, appears after intravenous injection of fat or not, and whether the fat intravenously injected is utilized by the organism or not, the following experiment was performed on depancreatized dogs given intravenous injections of fat emulsion.

(A) *Value of Total Serum Lipids.*

In totally depancreatized dogs, the total serum lipids were determined in a preliminary experiment prior to the intravenous administration of fat emulsion.

In totally depancreatized dogs, the average value of total serum lipids in 83 cases, determined early in the morning in a fasting state, was 543.96 ± 7.36mg per dl, whereas in 61 normal dogs it was 377.93 ± 6.06mg per dl.

Observation of the postoperative course of this lipemia showed that the value of serum lipids had already begun to increase on the 2nd postoperative day and reached its highest level within three to four weeks after operation and then gradually declined to somewhat higher level than that of the preoperative period and preserved this level thereafter (Fig. 2). Three or four weeks after operation, the dogs usually grew thin and finally the depot fat was almost exhausted.

This change in the value of total serum lipids after total pancreatectomy was in sharp contrast with its unchanged value

Fig. 2 Changes in the Value of Total Serum Lipids after Total Pancreatectomy (—), Subtotal Pancreatectomy (---) and Ligation of Pancreatic Duct (—·—)

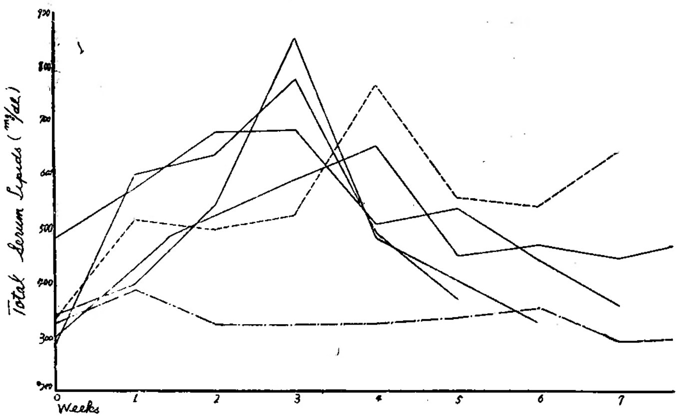
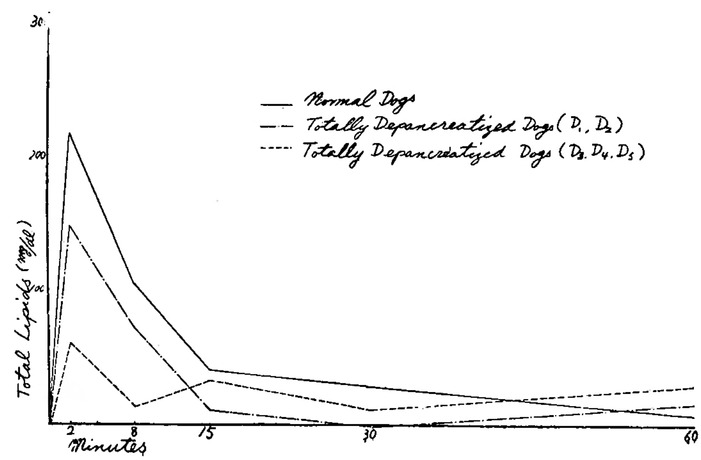


Fig. 3 Curves Showing Increments of Averaged Amounts of the Serum Total Lipids Following Intravenous Administration of Fat Emulsion in Totally Depancreatized and Normal Dogs.



after pancreatic duct ligation and to the maintenance of a high value after subtotal pancreatectomy.

(B) *Changes in the Value of Total Serum Lipids after Intravenous Fat Infusion.*

Eight per cent cod liver oil emulsion was used. The author injected 0.3g of fat per kg body weight into dogs through the hind leg vein taking 30 seconds in the morning in a fasting state and then removed 3cc of blood from the vein on the other side at intervals of 2, 8, 15, 30 and 60 minutes after injection, for the determination of the total serum lipids (Table 6, Fig. 3).

The dogs were given neither food nor insulin during the experiment.

In normal dogs, some showed uneasiness, vomiting and other signs of distress directly after injection. The blood removed 2 minutes after the injection was turbid and looked like chyle and the value of total serum lipids in it showed an increase of 100 to 300mg per dl. followed by a gradual decline to its previous level 1 hour after the injection.

When the fat emulsion was injected intravenously in totally depancreatized dogs within 2 days after the operation (D_1, D_2), signs of distress and an increase of total serum lipids also appeared just as in normal dogs.

When the infusion was performed in totally depancreatized dogs on the 3rd postoperative day or later (D_3, D_4, D_5), the value of

Table 6 Total Serum Lipid Levels Following Intravenous Administration of Fat Emulsion in Totally Depancreatized and Nomal Dogs

		Body Weight (kg)	Time after Operation	Fat Given Intravenously (g per kg)	Total Serum Lipids (preoperat.)	Time	Before Administration	After Administration (minutes) 2	8	15	30	60
Totally Depancreatized Dogs	D_1	6.2	30 Hours	0.3	(mg) 395.94	Total Serum Lipids (mg) (Increment)	561.52	694.66 (+133.14)	626.20 (+64.68)	555.40 (−6.12)	549.94 (−11.58)	555.40 (−6.12)
	D_2	12.0	30 Hours	〃	475.57	T. S. L. (I.)	496.19	661.58 (+165.39)	578.89 (+82.70)	525.72 (+29.53)	502.10 (+5.91)	531.63 (+35.44)
	D_3	7.5	3 Days	〃	395.94	T. S. L. (I.)	526.79	587.89 (+52.10)	555.73 (+28.94)	544.15 (+17.36)	538 36 (+11.57)	567.31 (+40.52)
	D_4	6.2	3 Weeks	〃	275.03	T. S. L. (I.)	450.63	527.72 (+77.09)	462.49 (+11.86)	502.10 (+51.47)	468.42 (+17.79)	468.42 (+17.49)
	D_5	6.3	9 Weeks	〃	486.74	T. S. L. (I.)	419.81	474.54 (+54.73)	419.81 (0)	450.23 (+30.42)	425.89 (+6.08)	450.23 (+30.42)
Normal Dogs	N_1	13.0		〃		T. S. L. (I.)	487.68	686.16 (+198.48)	561.40 (+73.72)	499.02 (+11.34)	476.34 (−11.34)	499.02 (+11.34)
	N_2	11.5		〃		T. S. L. (I.)	349.52	538.60 (+189.08)	441.19 (+91.67)	412.54 (+63.02)	424.00 (+74.48)	349.52 (0)
	N_3	8 0		〃		T. S. L. (I.)	344.26	605.23 (+260.97)	494.18 (+149.92)	391.23 (+49.97)	366.47 (+22.21)	355.36 (+11.10)

total serum lipids did not show so marked an increase as in normal dogs, and no signs of distress were observed after the injection. Although the serum became somewhat turbid 2 minutes after injection of fat emulsion, the value of total lipids did not increase more than 70mg per dl. and returned to its previous value within 30 minutes.

In Table 6 and Fig. 2, D_3 is the curve of hyperlipemia prouduced by the intravenous administration of fat emulsion on the 4th day, D_4 in the 3rd week and D_5 in the 9th week after total pancreatectomy. It is note-worthy that the forms of these curves are all almost identical, regardless of the time when the experiment was carried out.

(C) *Histochemical Findings in the Liver after Intravenous Fat Infusion*

In order to clarify the fate of the infused fat, which disappeared from the blood stream so rapidly in depancreatized dogs, the author examined the histochemical findings of the liver stained by sudan III at intervals of 2, 8, 15, 30 and 60 minutes after the infusion of fat emulsion under isomythal anesthesia (Plates).

In depancreatized dogs, Kupffer's cells take up a large amount of fat as early as 2 minutes after the infusion and these cells are filled with a maximum amount of fat within 15 minutes and begin to release the fat as early as 30 minutes after the infusion.

In normal dogs, however, only a small amount of fat appears in the Kupffer's cells 2 minutes after the infusion and a large amount of fat still remains in these cells 30 minutes after the infusion.

From these data, it may be said that in depancreatized dogs the fat introduced into the blood stream is managed physically faster than in normal dogs, because the value of total serum lipids does not increase so high after infusion of fat as in normal dogs, and because the liver of depancreatized dogs take up the introduced fat much faster than the liver of normal dogs.

(D) *Changes in the Amount of Fat Excreted in the Feces after Intravenous*

Table 7 Excreted Fat in the Feces Following Intravenous Administration of Fat Emulsion in Totally Depancreatized and Normal Dogs

	Body Weight kg	Days after Operation	Amount of Injected Fat		in the Feces before Injection		in the Feces during Injection		in the Feces after Injection	
			g per kg	Total (g)	Amount of Feces Daily (g)	Total Lipids Daily (g)	Amount of Feces Daily (g)	Total Lipids Daily (g)	Amount of Feces Daily (g)	Total Lipids Daily (g)
Totally Depancreatized Dogs	10.0	20	0.3	3.00	65.5	2.589	78.3	2.736		
	10.0	17	0.3	3.00	54.0	2.863	49.8	2.671		
	8.7	12	0.3	2.61	51.0	2.952	53.2	2.741	51.7	2.544
	8.0	28	0.6	4.80	40.8	2.424	49.2	2.250	58.8	2.417
	13.5	7	1.0	13.50	70.5	3.040	61.7	2.790	45.3	2.032
	12.5	15	1.5	18.75	52.0	2.568	33.0	2.037	30.0	1.414
Normal Dogs	6.5		0.3	1.95	13.5	0.547	13.0	0.436	12.0	0.389
	6.0		0.3	1.80	15.8	0.571	9.0	0.341	13.5	0.742
	6.5		0.3	1.95	22.7	0.674	14.8	0.384	14.0	0.571

Administration of Fat Emulsion

A test diet was given to dogs. Various amounts of fat ranging from 0.3 to 1.5g per kg body weight in a form of 8 % fat emulsion were injected once a day for 3 days into the dogs, and the feces excreted by each dog before, during, and after the injection were collected.

Contrary to my expectation (Table 7), the amount of fat excreted in the feces increased neither in depancreatized dogs nor in normal ones, in spite of the intravenous administration of fat. Therefore, it may be said that the fat which is infused into the blood stream does not appear in the feces even after total pancreatectomy.

(III) STUDIES ON TOTAL KETONE BODIES AFTER TOTAL PANCREATECTOMY

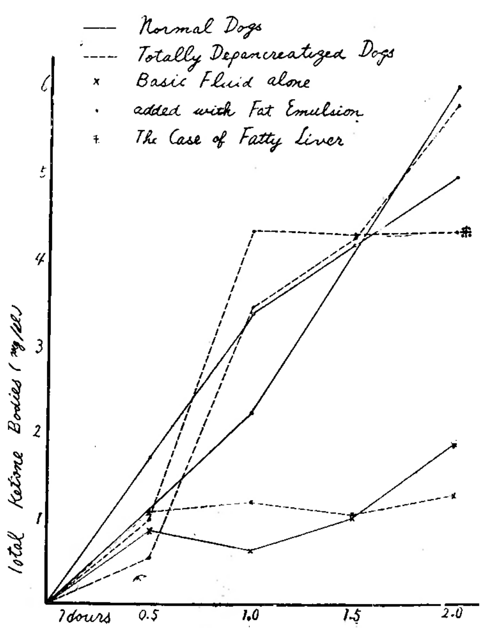
(A) *Ketone Bodies Formation in Isolated Perfused Liver.*

The dogs were fed a diet which contained no pancreatin, methionin and V. B_1 for 1 or 2 weeks after total pancreatectomy. Without using anesthesia the animals were killed by bleeding from the femoral artery, and then, the liver was isolated from the surrounding tissues as quickly as possible and a glass cannula was inserted into the portal vein and inferior vena cava. The blood in the liver was washed out slowly with approximately 300cc of modified RINGER-LOCK solution. If a part of the isolated liver gave a dark red-brown color, this liver was not used for examination because there by the coagulation of blood was suggested.

The isolated liver was perfused with OHASHI's closed circulator for 2 hours by the method of SENŌ and HASHINO. Defibrinated blood of the animal whose liver was isolated was diluted 2 times with modified RINGER-LOCK solution. 150 or 200cc of this diluted blood was used as the circulating fluid (basic fluid).

When the liver of depancreatized dogs, as well as that of normal ones, was perfused with the basic fluid mixed with fat emulsion (100 : 1.3), total ketone bodies in the perfused fluid increased markedly and amounted to 4.5 to 6.5mg per dl. 2 hours after the beginning of the perfusion and did not show a definite difference between these two groups of dogs (Fig. 4). In only one case (※) which was kept alive for 1 week after total pancreatectomy there was ketonemia and fatty infiltration of the liver at autopsy, and the total ketone bodies in the

Fig. 4 Changes of the Total Ketone Bodies in Circulating Fluid in the Isolated Perfused Liver.



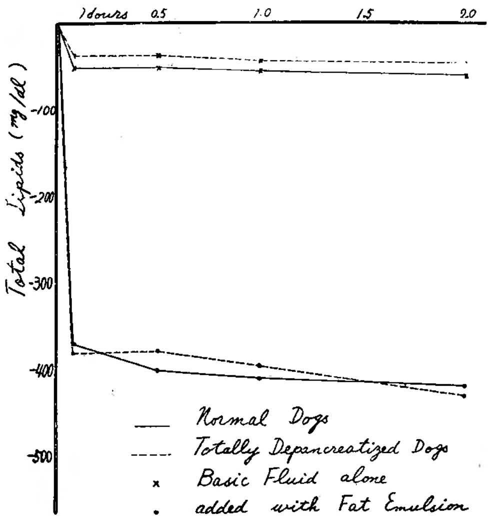
perfused fluid increased to 4.3mg per dl. 1 hour after the beginning of the perfusion, showing no increase thereafter.

When the liver was perfused with the basic fluid alone, total ketone bodies in the perfused fluid did not increase much and showed only an increment of 2 mg per dl. 2 hours after the beginning of the perfusion in totally pancreatectomized dogs as well as in normal dogs.

On the other hand, it was found that the amount of total fat in the perfused fluid decreased markedly 5 minutes after the beginning of the perfusion (Fig. 5).

It may be said that the fat disappearing from the perfused fluid was utilized to produce ketone bodies not only in normal dogs, but in depancreatized ones too.

Fig 5 Changes of the Total Lipids in Circulating Fluid in the Isolated Perfused Liver.

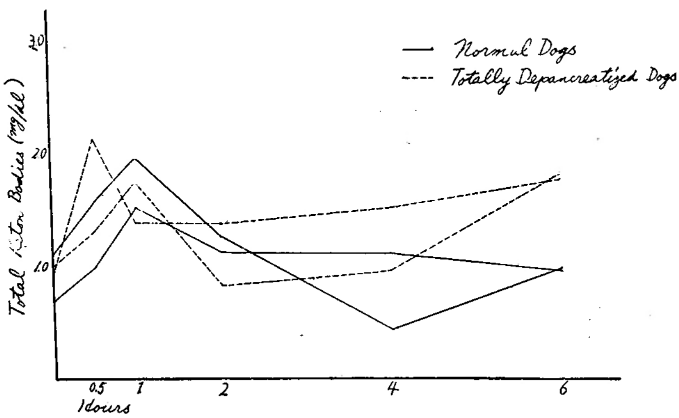


(B) *Changes in the Value of Ketone Bodies in Blood after Intravenous Administration of Fat Emulsion.*

From the results obtained by the preceding perfusion experiment it is evident that the formation of ketone bodies does not show any difference between the normal dogs and the depancreatized ones. In order to determine whether or not ketone bodies accumulate in the blood after intravenous administration of fat emulsion, the total ketone bodies in blood were determined (Fig. 6).

Eight per cent sesame oil emulsion was used. 0.5g of fat per kg body weight was injected intravenously, and then 1cc of the blood was removed at intervals of 30 minutes and 2, 4, and 6 hours after injection. Neither food nor insulin was given to the dogs during the experiment.

Fig. 6 Changes of the Total Ketone Bodies in Blood Following Intravenous Administration of Fat Emulsion.



In depancreatized dogs as well as in normal dogs, the total ketone bodies in the blood showed an increase of 1mg per dl. 30 minutes or 1 hour after the injection and thereafter fluctuated within a normal range. It was confirmed that there was no difinite difference in the level of the ketone bodies between normal dogs and depancreatized ones after the intravenous infusion of fat.

DISCUSSION

The process of intermediary metabolism of fat has not yet been completely clarified, especially in cases of diabetes mellitus. Since Krebs publicized the T. C. A. cycle theory, it has generally been considered that the terminal process of the intermediary metabolism of fat also enters into the T. C. A. cycle.

After total pancreatectomy, although abnormality of fat metabolism apparently receals itself in consequence of the occurrence of diabetes mellitus and of the total loss of pancreatic juice, it is not clear whether or not fat is metabolized to acetone bodies which then enter into the T. C. A. cycle. Moreover, in discussing fat metabolism, Dragstedt believes that the presence of hormone in the pancreas is essential.

From the results of my present experiments, I have found that the average amount of endogenous fat excreted in the feces of the totally depancreatized dogs increased to as much as 2.729g per day. As Partine et al. reported that the amount of endogenous fat in patients with multiple peptic ulcers or ulcerative colitis also increased, it may not be correct to assume that the increase of the amount of endogenous fat should be ascribed entirely to total pancreatectomy. However, it may be admitted that the excretion of endogenous fat is the cause of fluctuation in the rate of fat absorption and also the cause of negative rates in some cases.

Assuming that a certain amount of endogenous fat is always excreted in the feces after the oral administration of any amount of fat, one should subtract the amount of endogenous fat from the total amount of excreted fat in the feces, in order to determine the more accurate absorption rate of fat after total pancreatectomy. When one calculates in this way, one finds that the absorption rate of fat becomes relatively constant at 62.53 to 72.57% regardless of the amount of ingested fat.

Next, the concentration of fat in the chyle after the oral administration of fat was determined by means of an artificial thoracic fistula. Although somewhat impaired after total pancreatectomy, the absorption of fat actually took place through the thoracic duct, even in a case in which a small amount of fat (3 g) was administered.

Dragstedt et al. reported that alimentary hyperlipemia did not appear in depancreatized dogs after oral administration of fat and that this nonappearance of normal hyperlipemia was doubtless due to the impaired and perhaps delayed absorption of fat, and that the pancreas played some role in the absorption of fat in some way other than through the digestive action of pancreatic lipase. In the present experiments on the concentration of fat in the chyle and on hyperlipemia in response to the intravenous administration of the fat emulsion, it was found that the lack of alimentary hyperlipemia in the depancreatized dogs was due not only to the impaired and delayed absorption of fat but also to the fact that the increase of total serum lipids did not occur in the depancreatized dogs so markedly as in normal ones, when fat was administered intravenously.

One of the reasons for the absence of hyperlipemia after intravenous infusion of fat was that the liver of the depancreatized dogs managed the introduced fat physically much faster than the liver of normal dogs.

Although LOMBROSIO and DACHÁ stated that depancreatized dogs eliminated in the feces 56.5 to 111.8% of the fat in an olive oil emulsion given intravenously, it was not the case in my experiments.

It was found that the function of forming ketone bodies in the liver of the depancreatized dogs was preserved almost equally with that of normal dogs regardless of the development of fatty liver and that abnormal ketonemia did not occur after intravenous administration of the fat emulsion.

CONCLUSION

1. In totally depancreatized dogs, the average amount of endogenous fat in the feces increased to 2.729g, whereas it was 0.597g in the controls.

2. In contrast to the wide fluctuations in the ordinary absorption rates of fat, the corrected rates, in which the amount of endogenous fat excreted in the feces was taken into consideration, showed relatively constant values of 62.53 to 72.57% regardless of the amount of ingested fat.

3. Although somewhat impaired after total pancreatectomy, the absorption of fat actually took place through the thoracic duct. For example, even when a small amount of fat (3g) was administered orally, the fat was absorbed actually through the thoracic duct, whereas in this case the ordinary absorption rate of fat might give a negative value.

4. Marked postoperative hyperlipemia was observed for 3 to 4 weeks after total pancreatectomy, and then the fat content of the blood declined gradually to a somewhat higher level than that of the preoperative period and maintained this level thereafter.

5. In depancreatized dogs, the value of total serum lipids after intravenous fat infusion did not show such a marked increase as in normal dogs, and the fat introduced into the blood stream was taken up more rapidly by KUPFFER's cells after total pancreatectomy. The effect of the intravenously administered fat was the same regardless of the value of hyperlipemia incurred by pancreatectomy.

6. It was not confirmed that the fat administered intravenously to pancreatectomized dogs is eliminated in the feces (as stated by LOMBROSIO et DACHÁ).

7. The function of formation of ketone bodies in the liver was found to be preserved almost normally after total pancreatectomy and abnormal ketonemia did not occur after the intravenous administration of fat emulsion.

8. In depancreatized dogs, the fat administered orally or intravenously can be utilized with the administration of an adequate amount of insulin.

In closing, I wish to thank Prof. Dr. CHISATO ARAKI and Assist. Prof. Dr. ICHIO HONJO for their guidance throughout the period of this work. I am indebted also to Dr. HIKASA of the 2nd Surgical Division, Kyoto University, for his valuable advices.

Fig. 7 The liver before injection of fat emulsion in a normal dog.

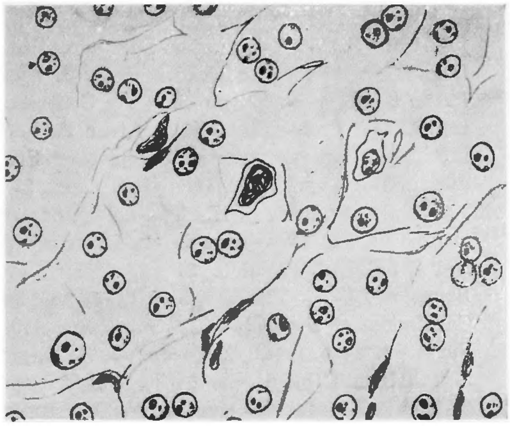


Fig. 10 The liver before injection of fat emulsion in a totally depancreatized dog.

Fig. 8 2 minutes after injection in the same dog as in Fig. 7. KUPFFER's cells take up a little amount of fat.

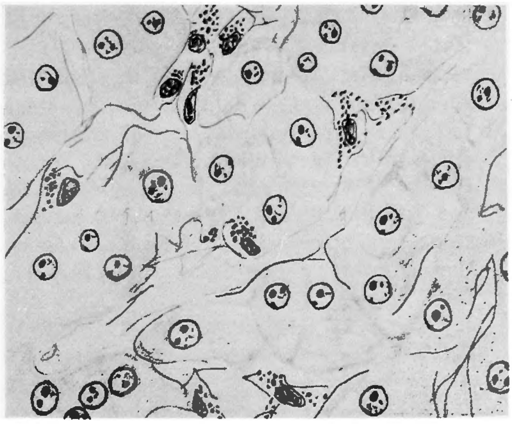


Fig. 11 2 minutes after injection in the same dog as in Fig. 10. KUPFFER's cells are filled with fat.

Fig. 9 30 minutes after injection in the same dog as in Fig. 7. KUPFFER's cells are filled with fat.

Fig. 12 30 minutes after injection in the same dog as in Fig. 10. KUPFFER's cells begin to release fat.

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（和文抄録）

膵全剔後の脂肪代謝について

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膵全剔後には，膵外分泌の欠除，糖尿病の発現による脂肪代謝異常の外に，膵に何か脂肪代謝に関するホルモン様物質が存在し，膵剔出によつて，脂肪の代謝過程に欠陥を生じているかと云う事が問題であつて，脂肪肝発現の有無と関聯を有している．

私は膵全剔犬に於て，経口的，経静脈的に脂肪を投与し，その代謝相を追及し，次の如き結果を得た．

1）全剔犬に貧脂肪食餌を投与した際糞便中に排泄される内因性脂肪量は，平均 2,729g であり，正常犬 0.597g に比し非常に増加している．

2）従来，膵全剔犬の脂肪の消化吸収率は，非常に変動し，時には負吸収率を示しているが，前記内因性脂肪量が，脂肪含有食飼投与の際にも排泄されていると仮定して，消化吸収率を補正すれば，62.53～72.57％と云う一定した吸収率を示すのを認めた．

3）膵全剔犬に於て，胸管よりの脂肪の吸収は，正常犬に比し低下はしているが，従来負の吸収率を示していた小量（3 g）の脂肪投与に於ても，明かに吸収が行われているのを認めた．

4）膵全剔犬は，術後3～4週を頂点とする顕著な脂肪血症を呈し，次第に術前に返る．

5）膵全剔犬に於ては，経静脉性脂肪注入により，正常犬に比し，血清脂肪増加を呈する事少く，注入脂肪も，より速に肝星細胞に摂取される．この注入脂肪の態度は，術後脂肪血症の高低に関係なく同様であつた．

6）Lombrosio 及 Dachá の云う如く，経静脉性に注入した脂肪が，糞便中に排泄されると云う事は認めなかつた．

7）膵全剔後，肝臓に於けるケトン体生成能は，脂肪肝の有無に関せず保持されており，且又，経静脉性脂肪注入により，ケトネミーを来す事もなかつた．

8）膵全剔犬に於て，経口的，経静脉的に投与された脂肪は少くともインシュリン投与等によつて糖代謝の様相をさえ改善すれば充分燃焼利用されると考えられる．