STUDIES ON THE LATER TYPE OF FATTY LIVER OF THE INSULIN-TREATED COMPLETELY DEPANCREATIZED DOG

by

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Since the report of MEHRING and MINKOWSKI[1], it has been known that the completely depancreatized dog receiving no insulin, dies several days after the operation due to the development of diabetes, and at the autopsy, an extreme degree of fatty infiltration and degeneration is found.

DRAGSTEDT[2] suggested that this type of fatty liver might be diabetic in origin because it occurred when the amount of insulin administered was not sufficient, and because it was accompanied simultaneously by hyperlipemia and ketosis.

In our clinic, OSHITANI[3] demonstrated that this diabetic or early type of fatty liver could not be prevented with the already known lipotropic substances such as methionine and vitamine B_{12}, but could be prevented by the administration of an adequate dose of insulin, which is probably over 1 unit per kg of the body weight a day.

On the other hand, FISHER[4], ALLAN, BOWIE, MACLEOD and ROBINSON[5] observed that a depancreatized dog did not survive more than a month after the operation, even if its diabetes was controlled with insulin, and that an extreme degree of fatty liver was found at the autopsy.

In this report, I will call the non-diabetic fatty liver "the later type of fatty liver", although the diabetic fatty liver is commonly called "the early type of fatty liver".

Since MACLEOD[6] proved that the non-diabetic fatty liver could be prevented by feeding it with raw pancreas, the pathogenesis of the later type of fatty liver has been gradually clarified by many investigators in the analytical studies of the beneficial effect of raw pancreas.

CHAIKOFF et al. demonstrated that the fatty liver of the completely depancreatized dog maintained with insulin could be prevented by the administration of one of the following: (1) fresh pancreatic juice[7][8][9][10] (2) methionine[11][12] (3) hydrolyzed casein[12] (4) crystalline trypsin[13] (5) a fraction derived from raw pancreas by the above mentioned physiologist[10][14][15]. According to these facts, they concluded that the antifatty-liver effect of raw pancreas could be attributed to its proteolytic enzymes, and that the development of such fatty liver was due to an interference in the mechanism whereby methionine of protein was made available for lipotropic purposes.

However, DRAGSTEDT et al. arrived at a different conclusion. As a result of

their investigations, the fatty liver of the completely depancreatized dog could be prevented not by the administration of fresh pancreatic juice[16][17], but by the administration of "lipocaic" which they extracted from raw pancreas and assumed as a specific substance, like a hormone, excluding lecithin, choline, or proteolytic enzymes [18]~[23]; they concluded that the fatty liver must be caused by the deficiency of "lipocaic".

Contrary to these investigators, AOKI[24] in our clinic observed that the insulin-treated completely depancreatized dogs did not show any fatty change of the liver for more than four weeks after the operation, no matter whether they had received pancreatin and methionine or not, and he assumed that such discrepancy between his observations and those of the others, might be caused by the difference of the digestibility of protein in the diet, because the well-cooked rice-barley-fish diet used in his experiments was probably more easily digestible than the raw meat diet used in foreign laboratories. The results of the experiment of RALLI et al.[25] that fatty liver which never fails to develop if fed with the raw meat diet can also be prevented if the dogs are fed with the dried meat powder, will support AOKI's assumption.

In this report, I have attempted to clarify the pathogenesis of the later type of fatty liver observed in a completely depancreatized dog treated with insulin, and have also stated the influence of the quality of the diet, and the dose of insulin upon the amount of liver lipids.

METHOD OF EXPERIMENT

(1) Adult dogs, both male and female, were used for this experiment.

(2) The operation was performed as follows: Under anesthesia of an intravenous injection of isomital sodium (0.05g/kg), an upper median incision was made. The pancreas was then freed from the duodenal wall (meticulous care being taken not to injure the pancreatico-duodenal vessels) and was completely extirpated.

(3) Experimental animals were fed twice daily. As a rule, 2 units of insulin per kg of the body weight a day were divided into two portions and given at each meal.

(4) Fasting blood sugar was determined by the SOMOGYI-NELSON'S METHOD[26].

(5) Total cholesterol and esterified cholesterol of the serum in the postabsorptive state were determined by the acetic anhydride method[27] and from these values, the cholesterol ester ratio was calculated. It was my hope that the ratio would indicate the development of fatty liver during the dog's life since CHAIKOFF and KAPLAN[28] had reported that the ratio lowered to zero when fatty liver developed.

(6) In some cases, concentration of the total fatty acids in the serum in the postabsorptive state was determined by KIK and SMITH'S Method[29].

(7) The liver fat was detected not only by the Sudan III stain[30] histochemically, but also measured chemically by the determination of total fatty acids by the VAN DE KAMER'S A Method[31].

RESULTS

I. Liver Lipids of the Insulin-Treated Completely Depancreatized Dogs Fed with the Rice-Barley-Fish Diet

At first, I reinvestigated whether the insulin-treated completely depancreatized dog fed with the well-cooked rice-barley-fish diet would not show an intensive fatty liver as Aoki's report had stated. As it is said that the later type of fatty liver which occurs even though insulin is administered, develops more than four weeks after the operation, in this experiment also the existence of fatty liver was examined more than four weeks after the operation. Moreover, in order to make sure that the fatty liver which is detected in the later period is not a protracted process of the early diabetic type of fatty liver, the liver fat of twelve dogs maintained with 2 units/kg of insulin and fed with the same diet, was examined during a period of two to four weeks after the operation and the results are summarized in Table 1. At the autopsy the amount of total fatty acids of the liver which ranged from 2.02% to 2.92%, gave an average of 2.50%. At the time of the operation, the values of the liver fat which ranged from 1.87% to 3.03% gave an average of 2.45%. Also by histochemical examination, there was no difference to be mentioned between the findings at the operation and those at the autopsy. These results indicate that under the administration of 2 units/kg of insulin, the completely depancreatized dog does not produce the diabetic fatty liver before four weeks after the operation. In other words, the fatty liver which develops under administration of 2 units/kg of insulin is decisively non-diabetic.

After this preliminary study, the liver lipids of the completely depancreatized dogs which were given 2 units/kg of insulin together with the rice-barley-fish diet

Table. 1 Liver Lipids of the Completely Depancreatized Dogs Fed with the Rice-Barley-Fish Diet and Survived from 2 to 4 Weeks after the Operation.

Dog No.	Period of survival (days)	Total fatty acids (%)	
		At operation	At autopsy
20	19	2.83	2.92
32	14	2.82	2.48
48	14	2.39	2.61
50	18	3.03	2.84
54	15	2.54	2.69
62	23	2.01	2.92
66	16	2.52	2.20
70	23	2.95	2.18
74	24	2.13	2.51
78	26	1.87	2.02
104	25	2.20	2.35
106	19	2.12	2.28
Average		**2.45**	**2.50**

Table. 2 Liver Lipids of the Insulin-Treated Completely Depancreatized Dogs Fed with the Rice-Barley-Fish Diet and Survived more than 4 Weeks after the Operation

Dog No.	Period of survival (days)	Body weight (kg)		Total fatty acids (%)		Pemarks
		Initial	Final	At biopsy	At autopsy	
5	41	6.6	3.4	2.28	2.54	Died. Emaciate at time of death
6	33	11.0	7.2	2.90	2.87	Died. Insulin shock.
10	130	17.6	10.6	2.18	2.76	Sacrificed.
14	48	11.0	5.2	3.13	3.15	Sacrificed.

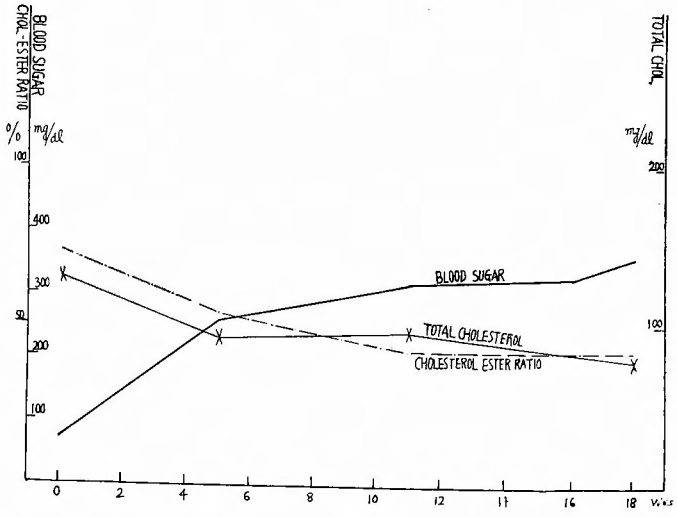

Fig. 1 The fasting blood sugar, total cholesterol, and cholesterol ester ratio in the serum of dog No. 10 after total pancreatectomy.

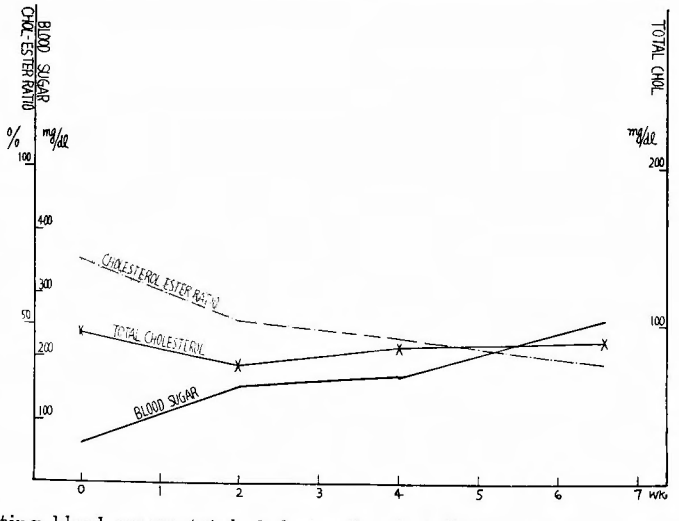

Fig. 2 The fasting blood sugar, total cholesterol and cholesterol ester ratio in the serum of dog No. 14 after total pancreatectomy.

Table. 3 Effect of the Feeding of Raw Whale Meat upon the Amount of the Liver Lipids of the Insulin-Treated Completely Depancreatized Dogs.

Dog No.	Period of survival (days)	Body weight (kg)		Total fatty acids (%)		Remarks
		Initial	Final	At biopsy	At autopsy	
8	43	16.5	9.7	2.28	2.81	Sacrificed.
12	39	11.4	7.3	2.43	2.17	Died. Ileus.
16	34	12.2	9.6	2.55	3.22	Met with accidental death.
18	30	6.6	4.8	—	2.52	Sacrificed.

and which had survived from 33 to 130 days after the operation, were examined. The results are tabulated in Table 2. All animals of this series, at the autopsy, did not show any fat-accumulation of the liver in both chemical and histochemical examinations. The postoperative courses of dogs No. 10 and No. 14 are illustrated in Fig. 1 and Fig. 2, respectively. In dog No. 10, a moderate decrease of total cholesterol, suggesting the presence of a slight hypolipemia, was observed, but in No. 14, it did not fluctuate much. In spite of the lowering of the cholesterol ester ratio to about 40%, fatty liver did not occur in all cases. The postoperative courses of dogs No. 5 and No. 6 resembled that of No. 10.

II. Effect of Raw Meat Diet upon the Liver Lipids of the Insulin-Treated Completely Depancreatized Dog

The liver lipids of the completely depancreatized dogs, maintained with 2 units/kg of insulin and fed with the raw meat diet instead of the rice-barley-fish diet, were examined.

(a) Effect of Raw Whale Meat Feeding——Four dogs were fed with 400g of raw whale meat a day together with small amounts of boiled rice, and their liver lipids were examined more than four weeks after the operation. The results are summarized in Table 3, and the postoperative courses of dogs No. 8 and No. 16 are illustrated in Fig. 3 and Fig. 4 respectively. The postoperative courses of these dogs resembled those of the dogs fed on the rice-barley-fish diet. The fasting blood sugar did not fluctuate much after rising to a certain hyperglycemic level. The total cholesterol decreased slightly, while the cholesterol ester ratio did not lower more than 40%. The amount of total fatty acids of the liver of this series, at the autopsy, ranged from 2.17% to 3.22% and all showed normal findings histochemically except one, in which only an enlargement of fat granules in the liver cells was found (Fig. 5).

(b) Effect of Raw Beef Feeding——The effect of the raw beef diet upon the development of the later type of fatty liver was studied. This mode of feeding is generally adopted in foreign laboratories. The raw beef diet used in my experiment was composed of 400g of raw beef (minced, and containing about 20% of crude fat), 400 cc of whole milk, and 100g of bread a day. This diet resembles that used by DRAGSTEDT et al.

The data obtained from the dogs who survived from 37 to 114 days after the

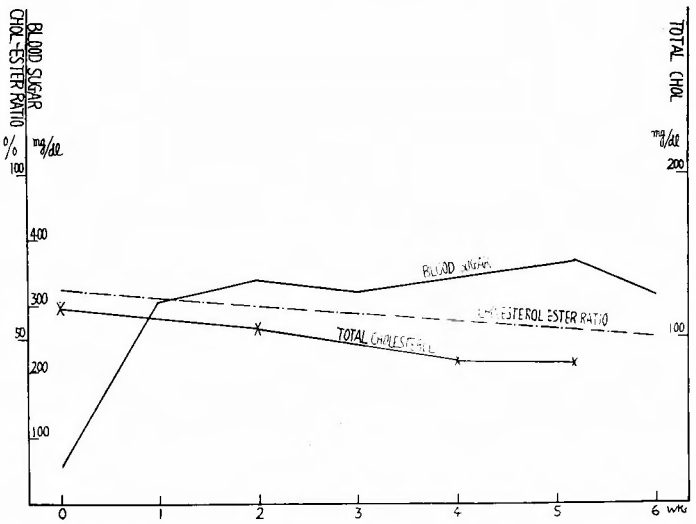

Fig. 3 The fasting blood sugar, total cholesterol and cholesterol ester ratio in the serum of dog No. 8 after total pancreatectomy.

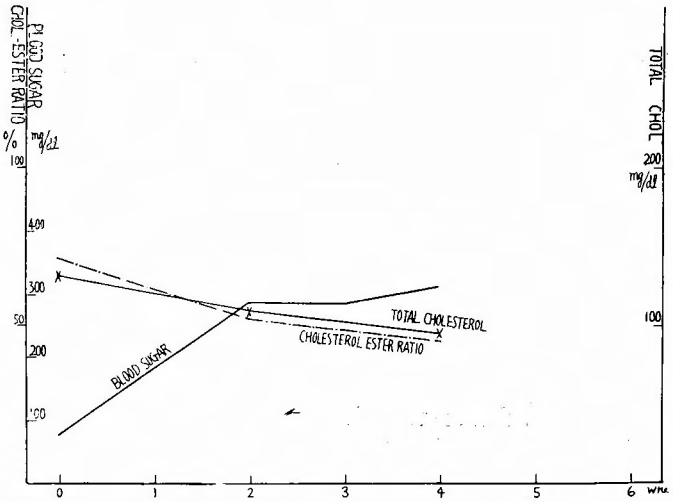

Fig. 4 The fasting blld sugar, total choleterol and cholesterol ester ratio in the serum of dog No. 16 after total pancreatectomy.

operation is summarized in Table 4. The amount of liver fat in these dogs increased, neither chemically nor histochemically except in one in which the total fatty acids slightly increased to 6.20%. The representative courses of this group following the operation are illustrated in Fig. 6 and Fig. 7. The cholesterol ester ratio of No. 120 which showed a slight degree of fatty infiltration did not lower less than that of No. 122 which showed no fatty change of the liver. This fact indicates that the cholesterol ester ratio can not denote the increase of the liver fat so clearly as CHAIKOFF et al. reported. Any way, even in the later period, and even though fed

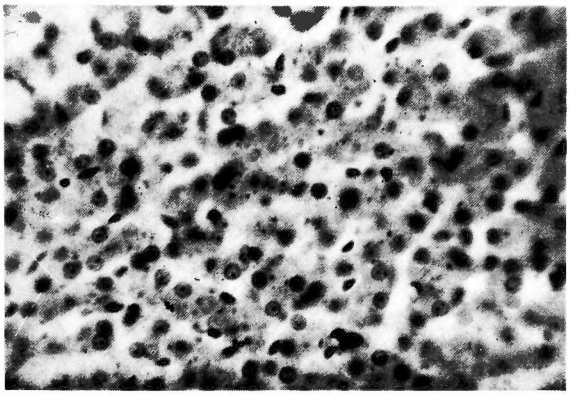

Fig. 5 Photomicrograph showing an enlargement of the fat granules in the liver-cells of dog No. 8 fed with raw whale meat. Sudan III stain. Magnification ×400

Table. 4 Effect of the Raw Beef Diet upon the Amount of the Liver Lipids of the Insulin-Treated Completely Depancreatized Dogs.

Dog No.	Period of survival (days)	Body weight (kg)		Total fatty acids (%)		Remarks
		Initial	Final	At biopsy	At autopsy	
108	37	9.0	6.7	—	2.92	Met with accidental death.
110	38	8.9	6.7	—	2.25	Died. Insulin shock.
120	61	10.0	7.8	—	6.20	Died. Insulin shock.
122	114	7.8	4.3	2.10*	2.65	Sacrificed.

* Biopsy was performed at the 70th postoperative day.

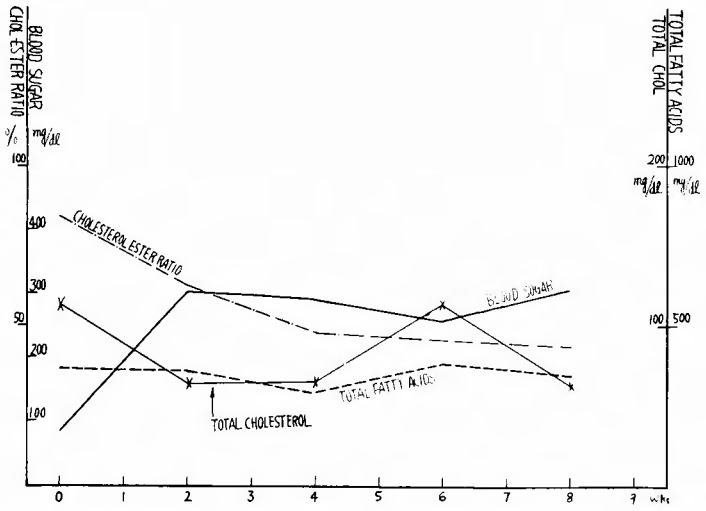

Fig. 6 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 120 after total pancreatectomy.

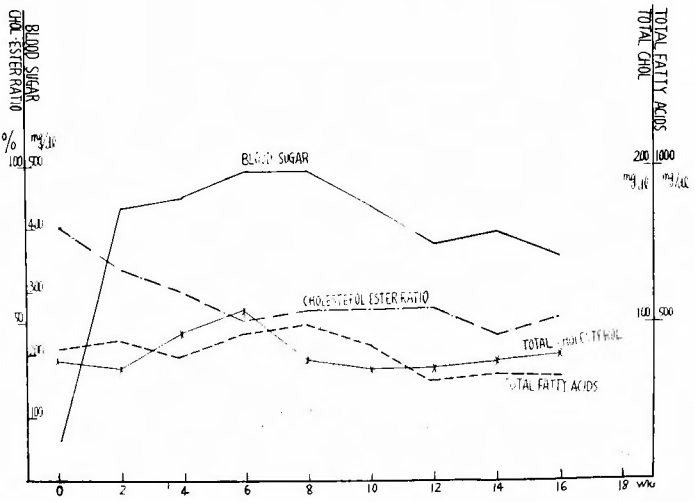

Fig. 7 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 122 after total pancreatectomy.

Table. 5 Effect of the Reduction of the Dose of Insulin upon the Liver Lipids of the Insulin-Treated Completely Depancreatized Dogs Fed with the Rice-Barley-Fish Diet.

Dog No.	Period of survival (days)	Body weight (kg)		Total fatty acids (%)		Remarks
		Initial	Final	At biopsy*	At autopsy	
34	37	10.6	6.9	2.90	**15.5**	Died.
84	37	11.5	6.6	2.61	**24.6**	Died.
64	39	11.8	7.4	2.52	2.16	Sacrificed.
82	62	9.0	5.8	2.18	2.23	Died. Insulin shock.

* Biopsies were performed at the end of the four week period after the operation.

with raw meat, the extreme degree of fatty liver did not develop in the insulin-treated depancreatized dogs. The 6.20% increase of the total fatty acids of the liver observed in dog No. 120 was so slight when compared with 35.5% increase reported by ALLAN et al.[5] and 29.7 to 45.7% as reported by CHAIKOFF et al.,[32], that this increase can not be considered to have a significant import.

III. Effect of the Amount of Insulin upon the Liver Lipids of the Completely Depancreatized Dog

(a) Effect of the Reduction of Amount of Insulin After it had been verified that the dogs did not produce a fatty change of the liver at the biopsy by the end of the four week period after the operation, period during which the dogs had been given 2 units of insulin and had been fed on the rice-barley-fish diet, the dose of insulin was reduced to 1 unit/kg a day and then the liver lipids were determined at the autopsy. The results are tabulated in Table 5.

The dogs of this series can be divided into two types according to the general

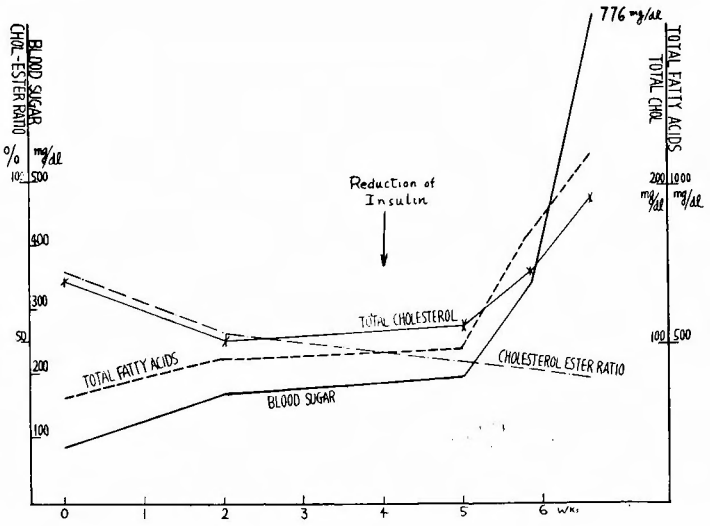

Fig. 8 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 34 after the reduction of insulin.

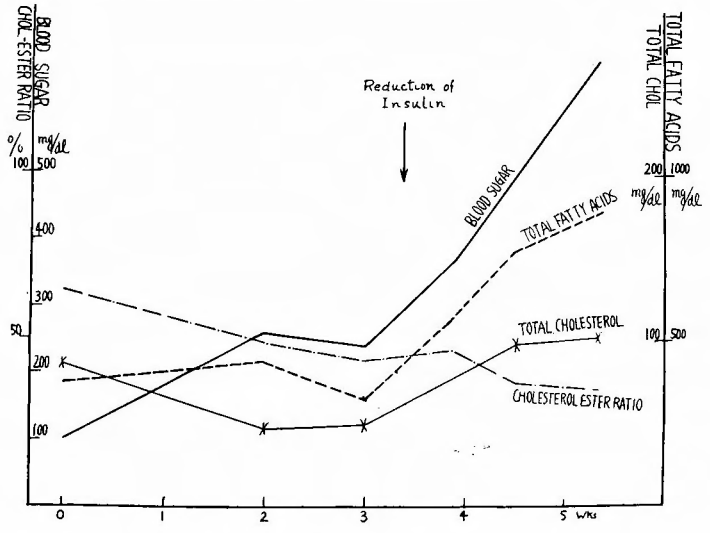

Fig. 9 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 84 after the reduction of insulin.

condition after the reduction of insulin, and the change of the amount of liver fat. After the reduction of insulin, dogs No. 34 (Fig. 8) and No. 84 (Fig. 9) lost their appetite, became emaciated and soon died. The fasting blood sugar and the serum lipids rose remarkably and total fatty acids of the liver increased to 15.5% and to 24.6% respectively. Histochemically, an extreme degree of accumulation of fat in the liver was found (Fig. 10, 11). In spite of this fact, the cholesterol ester ratio did not lower to zero but remained over 40%. This indicates that the ratio can not

be entitled to be an indicator of the development of the fatty liver as mentioned already. Dogs No. 64 (Fig. 12) and No. 82 (Fig. 13) showed different signs from those of Nos. 34 and 84 after insulin had been reduced; that is, the fasting blood sugar level and the concentration of the serum lipids not only rose, but in the case of No. 82, the blood sugar began to decline. Moreover, the general condition of these dogs did not change much even after the reduction of insulin; their appetite was kept relatively good and the fatty change of the liver was not observed in both cases.

(b) Effect of the Administration of a Small Dose (1 unit per kg) of Insulin after the Operation

The liver lipids of the dogs who had been fed on the raw beef diet and who had been given a small dose of insulin (1 unit/kg a day) were examined. The raw beef diet used was the same as stated above. The results are summarized in Table 6.

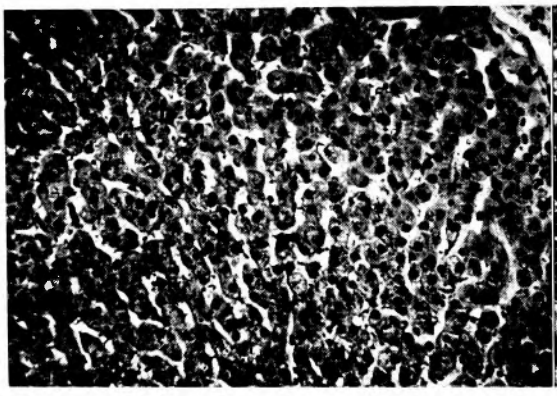

Fig. 10 Photomicrograph showing the extreme degree of fatty change in the liver of dog No. 34. Sudan III stain. Magnification ×200

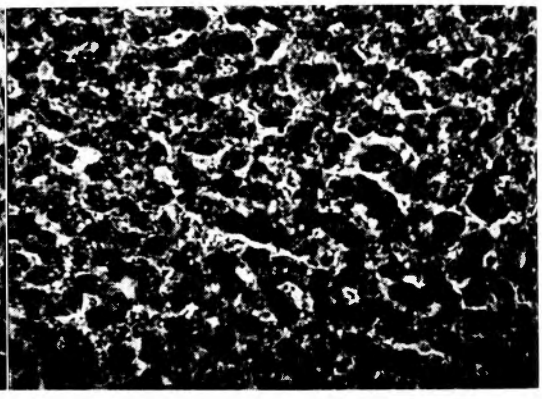

Fig. 11 Photomicrograph showing the extreme degree of fatty change in the liver of dog No. 84. Sudan III stain. Magnification ×200

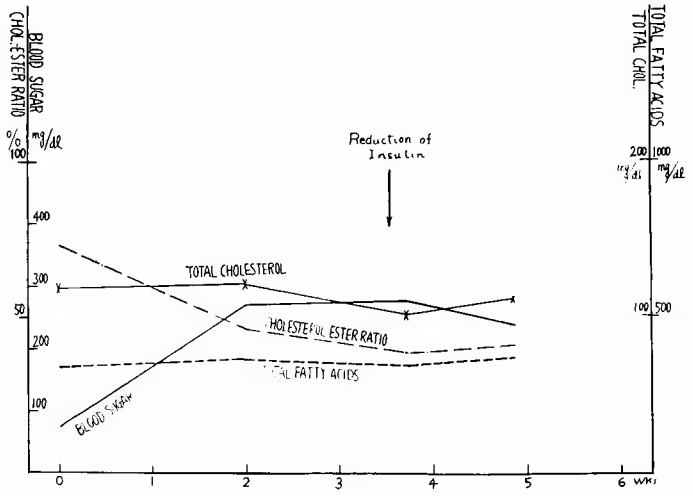

Fig. 12 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 64 after the reduction of insulin.

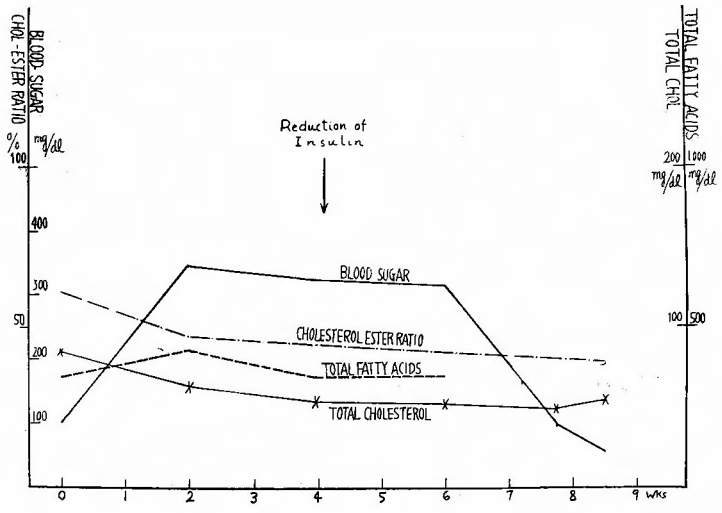

Fig. 13 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 82 after the reduction of insulin.

Table. 6 Effect of the Administration of a Small Dose of Insulin upon the Liver Lipids of the Completely Depancreatized Dogs Fed with the Raw Beef Diet.

Dog No.	Period of survival (days)	Body weight (kg)		Total fatty acids (%)		Remarks
		Initial	Final	At biopsy	At autopsy	
126	45	6.2	3.5	2.30	2.42	Died. Emaciated at time of death.
128	33	9.7	7.7	—	7.18	Sacrificed while in good condition.
132	30	8.1	6.4	—	2.11	Sacrificed.
134	28	6.0	4.8	—	2.87	Sacrificed

Fatty liver did not develop in the dogs of this series except in one which showed a slight fatty infiltration of the liver. Following the operation, the blood sugar level rose higher than those of the dogs receiving 2 units/kg of insulin at first, but within 1 or 2 weeks after the operation, it lowered and became about the same level as for the dogs who had received a larger dose. Both total fatty acids and total cholesterol of the serum rose with the marked rise of blood sugar immediately after the operation, but then decreased to about preoperative values. The cholesterol ester ratio always remained over 40% (Fig. 14, 15).

DISCUSSION

Almost all of the investigators who have studied the pathologic physiology of the completely depancreatized dog have always observed that an extreme degree of fatty change of the liver developed about a month after the operation, even if accompanying diabetes was adequately controlled with insulin, and they have made an effort to clarify the pathogenesis of this later type of fatty liver.

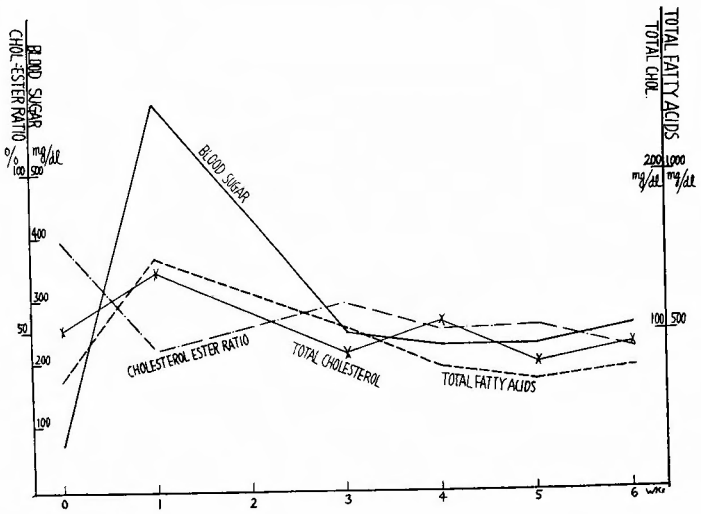

Fig. 14 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 126 after total pancreatectomy.

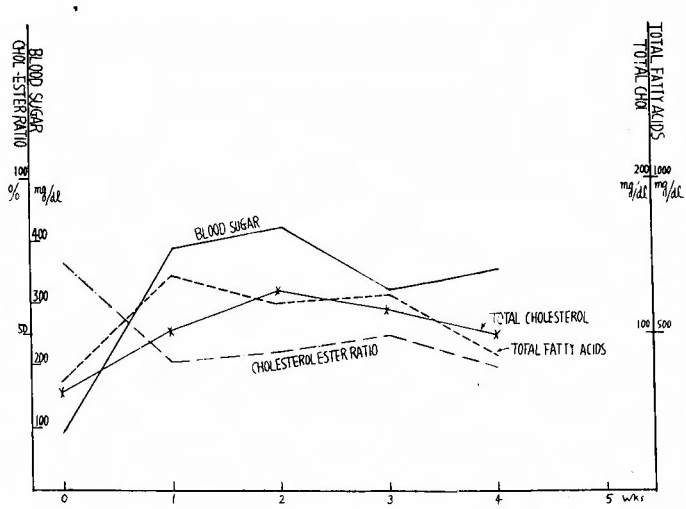

Fig. 15 The fasting blood sugar, total cholesterol, total fatty acids and cholesterol ester ratio in the serum of dog No. 134 after total pancreatectomy.

On the other hand, AOKI[24] in our clinic observed that the insulin-treated completely depancreatized dog did not produce such a later type of fatty liver and explained that the discrepancy between his results and others, might be attributed to the difference of their diet. In foreign laboratories, the animals were mainly fed with raw meat, while in AOKI's experiments, they were fed with the well-cooked rice-barley-fish diet. I then tried to elucidate the pathogenesis of the later type of fatty liver seen in the completely depancreatized dog by studying the effects of two important exogen factors, i. e., the dose of insulin and the quality of the diet upon

the development of the fatty liver in the later period.

The completely depancreatized dogs in my experiments which were given 2 units/kg of insulin a day to prevent the diabetic fatty liver, and fed with the well-cooked rice-barley-fish diet, did not produce a fatty liver after the operation. The results agree with AOKI's report. From these observations it is apt to be assumed that the later type of fatty liver seen in the completely depancreatized dog may be classified under the category of alimentary fatty liver as AOKI[24], RALLI and RUBIN[25] have stated. So, I concluded that a fatty liver would develop as it did in the foreign laboratories if the animals were fed with raw meat instead of the rice-barley-fish diet. But, unexpectedly, the dogs fed with raw whale meat failed to produce the later type of fatty liver even more than 4 weeks after the operation. Moreover, even in the dogs fed with raw beef, which contained about 20% of crude fat, the amount of liver fat was normal except in one in which a slight fatty infiltration of the liver was observed. The results indicate that the cause of the fatty liver seen in the later period after the operation can not always be attributed to the disturbance of the digestion of ingested protein due to the lack of pancreatic juice as CHAIKOFF et al.[15] and RALLI et al.[25] emphasized.

Then I investigated the effect of the reduction of the amount of insulin upon the liver fat contents. DRAGSTEDT reported that the insulin requirement of the animal did not lessen for one month after operation; then the dose of insulin had to be reduced to avoid fatal hypoglycemic convulsion which were considered to arise with the development of the fatty liver. A hypoglycemic convulsion was often observed during the present studies, but even when it happened, I continued to administer the usual dose, i. e. 2 units/kg of insulin with a large amount of glucose, and by this treatment, the animals were relieved from the hypoglycemic shock, and were able to come to receive the usual dose of insulin again. Furthermore, after the injection of the usual dose of insulin, no fatty change developed even in the dogs which had been attacked by a hypoglycemic shock.

As the next step, the amount of liver fat, after the reduction of the dose of insulin from 2 units/kg to 1 unit/kg 4 weeks after the operation was analysed. Among the four dogs of this series, two of them showed an extreme degree of fatty liver, while the others did not show any fatty changes. Because the fasting blood sugar and the serum lipids increased greatly, it was presumed that the dogs in which an intensive fatty liver developed, probably required as much as 2 units/kg of insulin throughout their lives; but the other dogs in which the fatty liver was not found, the insulin requirement had already been lessened to the small amount of 1 unit/kg.

Although the fatty liver provoked by the sudden reduction of insulin is considered to be diabetic in origin, it may be possible that some one misconceived this fatty liver for "the later type of fatty liver", because the dogs had still received an amount of insulin sufficient to prevent the early diabetic type of fatty liver, although the dose was reduced.

Since it was confirmed, as stated above, that the effect of the reduction of insulin upon the liver fat could not be disregarded, even in the later period, we then

studied the change which would take place in the liver fat if only 1 unit/kg of insulin was given after the operation. The liver fat of the dogs in this series which survived more than four weeks was, however, normal except in one, in which the total fatty acids of the liver came up to 7.18%.

It seems curious that in spite of the fact that the fatty liver developed in cases in which the dose of insulin was reduced suddenly from 2 units/kg to 1 unit/kg., the liver fat was found almost normal in the cases in which 1 unit/kg of insulin was administered after the operation.

These facts suggest that the development of the fatty liver may be accelerated by the sudden reduction of the amount of insulin rather than by the smallness of the absolute amount. In other words, it may be said that the depancreatized animal can manage to adjust themselves to the disharmony in metabolism so long as the amount of insulin administered was not changed.

SOSKIN et al.[33] stated that the function of the endocrine organs which counteract to insulin, plays an important roll on the insulin requirement or on the adaptation mechanism in the depancreatized dog. SHODA[34] in our clinic also demonstrated that the hypophyseal function of the subtotal depancreatized dog, that is, SANDMEYER's dog kept on in an almost normal condition, as long as a sufficient dose of insulin was administered, but the function lowered remarkably if the dose of insulin was inadequate. These observations interested me because they proved the close interrelation between the anti-insulin activities of the endocrine organs and the insulin requirement.

My experiments confirmed that the later type of the fatty liver of the completely depancreatized dog, regardless the quality of its diet, did not develop following the operation so long as an adequate dose of insulin, which was probably about 2 units/kg a day, was invariably administered. I should say, therefore, that the development of the fatty liver in the later period might be attributed to a disturbance of the metabolism which is brought about by the lack of balance between the exogen insulin and the activity of the anti-insulin system, especially hypophysis, rather than to the impaired digestion of ingested protein due to the lack of pancreatic juice.

Recently, GILLMAN and GILBERT[35] reported that fatty liver developed not only due to an absolute but also due to a relative insufficiency of insulin in the completely depancreatized baboon. This observation is interesting because it agrees with my conclusion, even though the animal used was not the same kind.

Since ROCKEY's efforts[36], the total pancreatectomy has been applied for clinical cases, such as cancer of the pancreas, islets adenoma, chronic pancreatitis, and so on. Many cases in which the patients lived several months or more after their operation without developing fatty liver, even if lipotropic substances had not been given, have already been reported[37)~48].

HONJO[49)50] in our country also reported that eight totally depancreatized men, surviving from a month to four years after the operation, did not show fatty changes of the liver except one who died from an acute aggravation of tuberculosis of the lungs which necessitated the reduction of insulin dosage.

We surgeons need not fear to perform a total pancreatectomy on a man in view of the fact that the complete depancreatization did not produce the later type of fatty liver not only in a dog, but also in a man.

It should be emphasized, however, that the early type of fatty liver, or the diabetic fatty liver will develop even in a later period after the operation if there is an absolute or a relative lack of insulin.

In the clinical cases also, it is irrational to reduce the dose of insulin in order to avoid a hypoglycemic shock which is often caused by a carbohydrate inanition, because the sudden reduction of insulin added to the carbohydrate inanition, will promote the development of a fatty liver as my experiments demonstrated. When a carbohydrate inanition is caused by an inveterate diarrhea or a loss of appetite which often happens after the total pancreatectomy, it is highly advisable to administer a great deal of glucose and also not to reduce the amount of insulin.

SUMMARY

1) Contrary to the reports of FISHER, DRAGSTEDT; AOKI in our clinic did not observe the development of fatty liver in dogs which were fed on the rice-barley-fish diet, even in a later period after the operation.

I reinvestigated whether the fatty liver would occur or not in the insulin-treated completely depancreatized dogs fed on the rice-barley-fish diet, and obtained the same results as appear on AOKI's report.

2) In spite of the feeding of raw meat which was used in foreign laboratories, instead of the rice-barley-fish diet, the dogs did not show the later type of fatty liver as long as they had received 2 units/kg of insulin. According to this observation I can not accept the theory of CHAIKOFF et al., or that of RALLI et al. that the development of the later type of fatty liver is solely attributable to the impaired digestion of protein due to the lack of pancreatic juice.

3) By the sudden reduction of the 2 units/kg dose of insulin to the 1 unit/kg, fatty liver developed four weeks after operation in half of the animals for the experiment. In the dogs which had received 1 unit/kg of insulin after the operation, however, fatty liver was not observed.

4) The means of preventing fatty liver in the completely depancreatized men was also discussed.

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和文抄録

膵臓全剔後の後期脂肪肝に関する研究

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膵臓全剔犬における従来の実験的研究によると，膵全剔後に発生する脂肪肝はその成因及び発生時期によつて2つに分類されている．

その一つは一般に早期脂肪肝と呼ばれており，術後におけるインシュリン投与が不充分で糖尿病が適切に治療されない場合に術直後より発生するものであり，従つて適当量のインシュリンを投与するならばその発生を完全に防止し得る．今一つは，適当量のインシュリン投与によつて早期脂肪肝を防止しても尚殆んど全例に術後約1ヵ月頃より発生する脂肪肝で，通常後期脂肪肝と称されている．

この後期脂肪肝の成因に関して Chaikoff 一派は，膵全剔後は膵液欠除のため摂取蛋白質の消化が不充分となり，従つてその含有するメチオニンを遊離して抗脂肝のために利用する機構が障害されることによると主張し，Dragstedt 一派は，彼らが膵臓から抽出し

た脂肪代謝促進物質たるリポカイックの投与が，後期脂肪肝の発生を予防乃至治療し得た実験成績から，リポカイック欠落が後期脂肪肝発生の原因であると強調している．

ところが，教室における実験では，膵全剔犬はよく煮た米麦魚食と適量のインシュリンを投与して飼育するならば後期（術後4週以降）においても脂肪肝を発生し難いという成績を得た．

本研究では，従来必発と考えられていた後期脂肪肝がわれわれの研究室では発生し難い理由を解明するために(1)食餌の性質，及び(2)インシュリン投与量，が膵全剔後後期における肝脂肪量に及ぼす影響を追究し，更に後期脂肪肝の成因にも言及した．

(1)インシュリン 2u/kg 投与米麦魚食飼育膵全剔犬の肝脂肪．

従来の教室の成績を追試して，インシュリン2u/kgを米麦魚食と共に投与飼育した膵全剔犬の肝脂肪をしらべたが，術後4週以前に於ても，4週以後に於ても全例に脂肪肝の発生を認めなかつた．

(2)生獣肉飼育がインシュリン投与膵全剔犬の肝脂肪量に及ぼす影響．

われわれが従来後期脂肪肝の発生を認めないのは，外国では実験犬に主として生の牛馬肉を与えるのに対して，われわれは米，麦，魚類をよく煮て与えるという飼育上の相違に帰因するのではなかろうか，即ち生獣肉で飼育するならば後期脂肪肝が発生するであろうと考え，インシュリン 2u/kg と共に生獣肉を与えて飼育した膵全剔犬の肝脂肪量を測定した．

(a) 生鯨肉を1日 400g 与えて術後4週以上生存した4頭は，予期に反して全例に肝脂肪の増加を認めなかつた．

(b) 生牛肉 400g，牛乳 400cc，パン 100g を与え術後37日乃至114日生存した4頭に於ても，1例に軽度の脂肪浸潤（肝総脂肪酸 6.20%）を認めた他はすべて正常であつた．

以上の如くインシュリンを 2u/kg 投与する限り，膵全剔犬は食餌の如何をとわず後期脂肪肝を発生し難い事実から，著者は Chaikoff らの膵液欠除による蛋白消化吸収障害説を全面的には肯定し得ないものである．

(3)インシュリン量が膵全剔犬の脂肪量に及ぼす影響

(a) インシュリン減量の影響——膵全剔後インシュリン 2u/kg を米麦魚食と共に投与して術後4週にいたり，生検によつて脂肪肝が発生していないことを確めた犬で，以後急激にインシュリンを 1u/kg に減量して肝脂肪量の変化をしらべた．このグループの4頭中，2頭は減量後急速に衰弱死亡し，剖検で著明な脂肪肝の発生を認めたが，他の2頭は減量後も肝脂肪量に変化を示さなかつた．脂肪肝を発生した犬は，血糖，血清脂質の著しい上昇を伴つたので，この脂肪肝は後期に発生したとはいえ，糖尿病性脂肪肝と理解すべきものと考えるが，しかし一般に膵全剔犬の早期脂肪肝防止に充分と考えられている量，即ち 1u/kg のインシュリンを尚投与しているので，これがいわゆる後期脂肪肝と見做される可能性は少くなかつたものと推測される．一方脂肪肝を発生しなかつた犬では，血清脂質，血糖は減量後も上昇せず，1u/kg のインシュリンでも尚糖尿病を適切に調節し得たものと考えられる．

(b) 少量インシュリン投与の影響——生牛肉400g，牛乳 400cc，パン 100g を与え，インシュリンは術後初めから 1 u/kg の比較的少量を投与したが，4週以上生存した4頭中1頭に軽度の脂肪浸潤（肝総脂肪酸 7.18%）を認めた他はすべて肝脂肪量の増加を来さなかつた．

インシュリンを 2 u/kg から急激に 1 u/kg に減量した場合には脂肪肝が発生するのに，初めから1u/kg 投与では発生しない事実は，脂肪肝発生に及ぼすインシュリン量の影響はその絶対量が少い場合よりもむしろ投与量の急激な減量が行われた場合に大きいことを示唆している．即ち脂肪肝は抗インシュリン的に働く内分泌系の機能と投与インシュリン量との平衡に破綻を来した場合に生ずるのであり，この平衡が保たれる限り，インシュリン量が比較的少量でも脂肪肝は発生し難いのであろう．

結　　語

(1) 膵全剔後の後期脂肪肝は，インシュリン2u/kgを投与し続ける限り，食餌がたとえ生獣肉であつても発生し難い．

(2) 後期における脂肪肝発生にもインシュリン投与量が抗インシュリン内分泌系機能との関係において重大な影響を与えるものである．