THE BLOOD SUGAR LEVEL AND THE DOSE OF INSULIN REQUIRED AFTER TOTAL PANCREATECTOMY (THE SENSITIVITY TO INSULIN)

by

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In 1924 FISHER, ALLAN and others reported that completely depancreatized dogs usually failed to survive for a long time, even if treated adequately with insulin, and a marked accumulation of fat in the liver was found to be the most prominent change in these dogs at autopsy. FISHER reported also that insulin probably did not represent the entire pancreas hormone complex, since in the total absence of the pancreas administration of insulin neither prolonged the life nor controlled all the diabetic symptoms.

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

Following this, DRAGSTEDT et al stated that the effect of oral administration of the raw pancreas to prevent the fatty liver was due to the function of an unknown hormone contained in the pancreas tissue, and he named this assumed hormone "lipocaic". He reported also that the fatty liver which appeared immediately after operation did disappear by the injection of insulin, while the fatty liver appearing 4 to 6 weeks later, could no more be managed with insulin and that in proportion to the decrease of urinary sugar the dose of insulin had to be reduced. 6 to 8 weeks after operation these dogs excreted only 1 to 2g. of urinary sugar daily, and the injection of only 2 to 3 units of insulin was enough to control the glucosuria, and in this stage administration of as few as 5 units of insulin resulted in fatal hypoglycemia. From these observations he concluded that the marked increase of the sensitivity to insulin was characteristic sign of the fatty liver caused by the lack of "lipocaic".

Against DRAGSTEDT, AOKI in our Clinic reported that in almost all dogs which survived for a comparatively long period after total pancreatectomy, a remarkable fatty liver did not take place despite the treatment with insulin only. He confirmed this fact not only macroscopically and histochemically but also by the determination of the actual amounts of fat in the liver.

In men, since ROCKEY (1943) had for the first time performed total pancreatectomy for pancreatic cancer, PRIESTLEY, BRUNSCHWIG, WAUGH, DIXON, CLAGETT, GASTON, FALLIS, GREENFIELED and others successfully did this operation for malignant tumor or chronic inflammation of the pancreas, and not a few of these patients

are surviving for a long time post-operatively. According to these reports the blood sugar level after operation tends to fluctuate and the sensitivity of the patients to insulin is markedly increased, consequently they often exhibit hypoglycemic signs. Thus it has been generally recognized that the insulin requirement of these patients is much less than that in clinical diabetics. However, there was none of these patients who presented signs of the fatty liver during life, and the fatty liver was confirmed at the time of autopsy in only 1 case (BRUNSCHWIG), but even in this case the cause of death was considered as diabetic coma, and therefore this fatty liver was probably the result of toxic degeneration following diabetic coma.

It is the purpose of the present study to know, whether the reduction in the dose of insulin to be administered in the post-operative course in dogs after total pancreatectomy is actually necessary or not ? And whether a marked increase of insulin sensitivity may truly occur after total pancreatectomy in men, and if so, what kind of mechanism may concern with ?

In order to make clear these problems, I have examined after total pancreatectomy in dogs and men, the blood sugar level in its relation to the dose of insulin administered in the post-operative course. And at the same time the insulin-test has been carried out to obtain additional evidences.

It is well known that the ketosis is apt to occur in severe clinical diabetics. On the other hand, it has been stated by many authors that the blood sugar level after total pancreatectomy should be kept in a considerably higher level than normal, as the sensitivity to insulin after operation is increased and thereby hypoglycemia easily develops. Consequently it would seem probable that the ketosis might frequently develop after total pancreatectomy. However, FALLIS stated that in totally depancreatized patients the ketosis did not occur as readily as one had expected, and urinary acetone body did not remarkably increase during 3 days of insulin withdrawal.

Therefore, in the present study the amount of blood acetone body was measured after total pancreatectomy both in dogs and men in order to examine whether the ketosis might develop.

Moreover the blood sugar level and the dose of insulin required after subtotal or partial pancreatectomy, or after ligation of the pancreatic duct were examined as control experiments.

MATERIALS

Adult dogs of about 10 kg. weight were used, after having been fed with a definite diet for more than a week. Blood sugar and blood acetone body were examined using the venous blood taken from a hind limb in animals and from a cubital vein in men early in the morning.

METHOD OF OPERATION

In total pancreatectomy in the literature the pancreas seems to have been extirpated alone, leaving the duodenum intact. However, the pancreas is anatomically so closely related to the duodenum in dogs as well as in human beings, that com-

plete removal of the pancreas without causing necrosis of the duodenum is nearly impossible. Accordingly, if one leaves even a small part of the pancreatic head attached to the duodenum, the post-operative physiology is not equal to that observed after completely total pancreatectomy. Therefore in my experiments the pancreas was removed in a lump with the duodenum and gastro-jejunostomy and choledocho-jejunostomy were added in animals as well as in men.

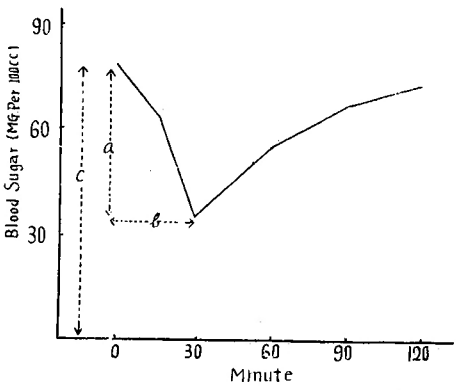
METHODS OF EXPERIMENTS

There has been generally adopted HAGEDORN-JENSEN's method to determine blood sugar, but this method has a fault likely to be influenced upon by reducing substances other than sugar in consequence of using ferri-cyanic salts in a reagent. In 1945 SOMOGYI published a new method with which the more accurate blood sugar determination was possible by using zinc-sulphate and barium hydroxide to make the protein-free filtrate and by adding anhydrous disodium phosphate and anhydrous sodium sulphate in a reagent. In my experiments, blood sugar was determined following this SOMOGYI's method with iodine-titrimetry using 1 cc of blood.

Blood acetone body was determined with TAKAHATA-KUME's method using 3 or 5 cc of blood. Aceto-acetic acid and β-hydroxibutric acid in the blood were oxidized and changed into acetone, and the latter was distilled and then determined quantitatively with the iodine method.

For the insulin test, regular insulin was always used, and in depancreatized dogs 0.1 to 0.3 unit of insulin per kg. body weight was injected intravenously, and in depancreatized men 10 units of insulin were uniformly injected subcutaneously. And then blood sugar was measured at certain intervals for 4 hours after the injection of insulin. As the amount of insulin to be injected in depancreatized dogs was very small, insulin was so diluted with the solvent provided by the Japanese pharmacopoeia that 1 unit of insulin was contained in 1 cc, in order to lessen the errors of the insulin dose as far as possible.

There are many methods to determine the sensitivity to insulin numerically, such as calculating the dimensions surrounded by the blood sugar curve, or measuring the absolute loss of glucose in the blood in milligram per cent, or showing the absolute loss of glucose in the blood per minute and others. I have adopted the "assimilation index" introduced by NORGAARD and THAYSEN, which seems to indicate the sensitivity to insulin with accuracy, taking the KUZUYA's view into consideration that the higher the blood sugar level in the state of fasting is in diabetics, the more sharply



$$\text{Assimilation Index} = \frac{a}{b} \times \frac{100}{C}$$

Fig. 1 Calculation of Assimilation Index (Norgaard and Thaysen)

the blood sugar level tends to drop, and the lower the fasting blood sugar level is, the less sharply it drops. The calculation in this method is shown in Fig. 1.

RESULTS

The blood sugar level of normal dogs in my experimental series ranged in the state of fasting between 81 mg. per 100 cc in maximum and 64 mg. in minimum, and the amount of acetone body in the blood is in the same state between 4.1 mg. per 100 cc in maximum and 1.4 mg. in minimum.

(I) TOTALLY PANCREATECTOMIZED ANIMALS AND MEN

Many investigators reported that after total pancreatectomy the blood sugar level became very unstable to the insulin administration, showing thereby a marked fluctuation, and sometimes even hypoglycemia.

MOSENTHAL stated, however, that hyperglycemia itself was not harmful to tissue-cells of the body, and also HIRAYAMA reported that if the blood sugar level was below about 300 mg. per 100 cc, there was no much harmful effect on various kinds of somatic cells. Moreover, it is widely accepted that hyperglycemia in diabetes is to be regarded as an "adaptation phenomenon" of the body for the deficiency of insulin.

Taking these facts into consideration, I have administered insulin in such an amount that the blood sugar level after total pancreatectomy (both in dogs and men) is kept constantly approximately 200 mg. per 100 cc.

(i) TOTALLY PANCREATECTOMIZED DOGS

Changes both in the blood sugar level and in the amount of blood acetone body without post-operative administration of insulin were illustrated in Fig. 2. Both curves ascended steadily, and all dogs in this experimental series died within 6 days. The acetone body level in the blood was unexpectedly low, probably due to the short survival of the animals after operation.

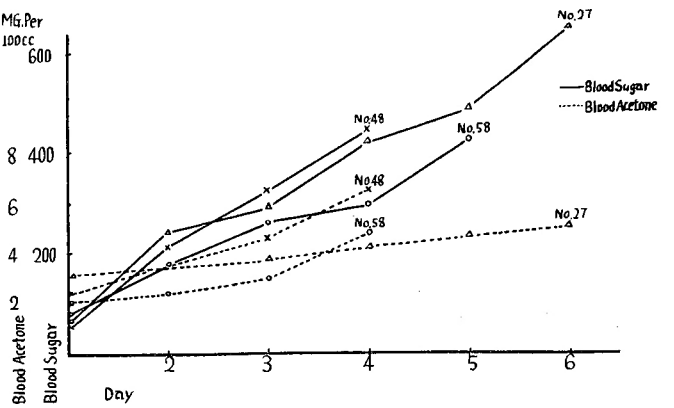


Fig. 2 Changes in the Value of the Blood Sugar and the Blood Acetone in Totally Depancreatized Dogs without Post-Operative Administration of Insulin

Among the dogs in which I controlled the blood sugar level by the insulin administration after total pancreatectomy, 23 dogs which had survived over 4 weeks post-operatively, were subjected to the following examinations. To 17 out of these 23 dogs, daily 2 g. of methionine and 5 g. of pancreatin were given. Remaining 6 dogs were control animals without receiving either pancreatin or methionine.

The amount of insulin administered to these animals was gradually increased

according to the recovery of their appetite after operation, and about 10 days later reached the almost constant dose, which was 30 units in maximum and 8 units in minimum, the average being 12～25 units.

In the further course, it was found that there were three types of the insulin requirement :

I Type ; As shown in Fig. 3, a considerable reduction of the insulin dose was necessary in the course of time.

II Type ; As shown in Fig. 4, there was no need to reduce the insulin dose throughout or for the most part of the postoperative course.

III Type ; cf Fig. 5. There was some necessity of reducing the insulin dose but not so markedly.

The cases belonging to I type were only 4 out of 23 dogs, and 11 dogs were classified in II type, and 8 in III type.

And among 23 dogs, the definite fatty liver was observed in only 1 belonging to I type, and in all other animals there was no fatty liver.

The relation between the

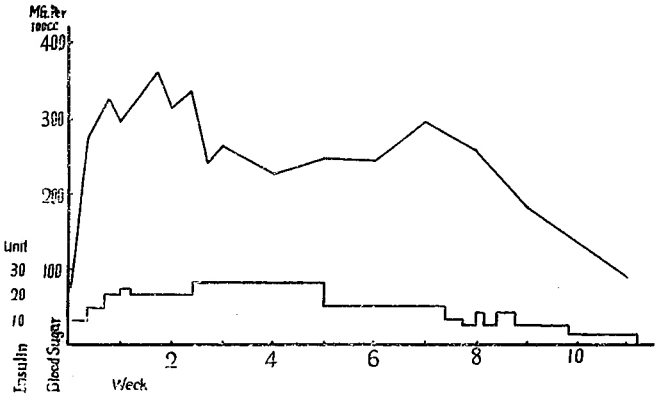


Fig. 3 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Totally Depancreatized Dog (No. 28). (Type I)

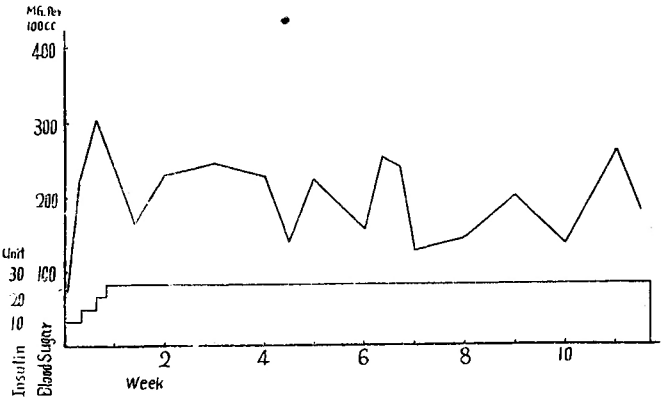


Fig. 4 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Totally Depancreatized Dog. (No. 18) (Type II)

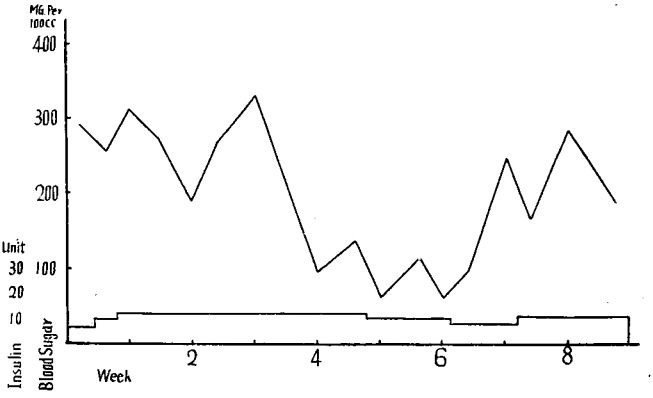


Fig. 5 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Totally Depancreatized Dog. (No. 82) (Type III)

administration of both pancreatin and methionine, and the dose of insulin required in the post-operative course was shown in Table 1.

The dogs in which more or less gradual reduction of the insulin dose was necessary after operation, in other words, cases belonging to I and III types, were 5 out of 6 dogs (83 %) in the group without administration of pancreatin and methionine, while they were only 7 out of 17(41 %) in the group with pancreatin and methionine.

The amount of acetone body in the blood after total pancreatectomy did not reach a high level, remaining almost always within 10 mg. per 100 cc, as far as blood sugar was controlled to a level near 200 mg. per 100 cc, as Table 2 shows.

Tadle 1 Relation between the Administration of Pancreatin and Methionine, and the Changes of the Dose of Insulin Required in Totally Depancreatized Dogs.

	Type I	Type II	Type III	Total
Cases with Pancreatin and Methionine Administration	2	10	5	17
Cases without Pancreatin and Methionine Administration	2	1	3	6

Table 2 Blood Acetone in Totally Depancreatized Dogs

Post-Operative Weeks	Blood Acetone (MG. per 100cc) Dog No.			
	No. 5	No. 8	No. 15	No. 18
1	——	——	17.8	3.1
3	4.6	3.9	——	3.5
5	7.1	5.8	——	5.5
7	7.7	7.1	——	——

(ii) TOTALLY PANCREATECTOMIZED MEN

In 5 patients we could follow-up their post-operative course over 1 month after operation.

Case 1 ; A woman aged 39. As illustrated in Fig. 6, the blood sugar level and the amount of blood acetone body 4 weeks after operation was 389 mg. per 100 cc and 21.7 mg. per 100 cc respectively. Thus both levels were extraordinarily high but by the gradual increase of the insulin dose the former could be kept around 200 mg. per 100 cc and the latter also in the normal range. At present, after 2 years and 11 months, her appetite is very sound, there is no change in the body weight, and the daily insulin requirement is almost always 25 units and there is no need of reduction of the insulin dose.

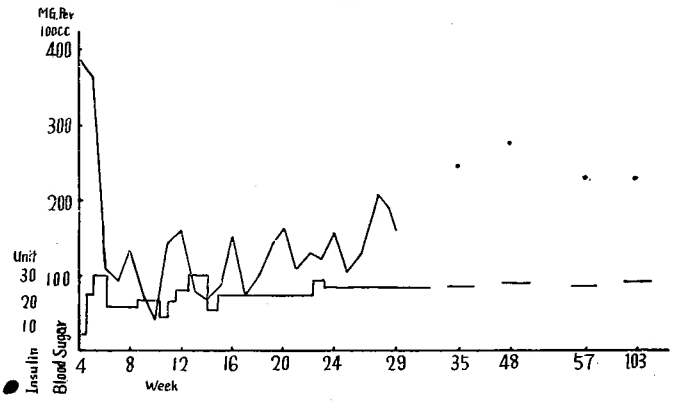


Fig. 6 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Totally Depancreatized Man. (Case 1)

Case 2 ; A woman aged 49. cf Fig. 7. During a certain period after operation, the condition of the patient was quite satisfactory, her appetite was good and the

daily insulin requirement was about 25 units constantly. From about the 8 th week after operation mild signs of intestinal obstruction did appear and appetite declined steadily, consequently the daily insulin requirement should be reduced gradually. She died finally after 142 days post-operatively and at autopsy progressive tuberculous changes were found in both lungs.

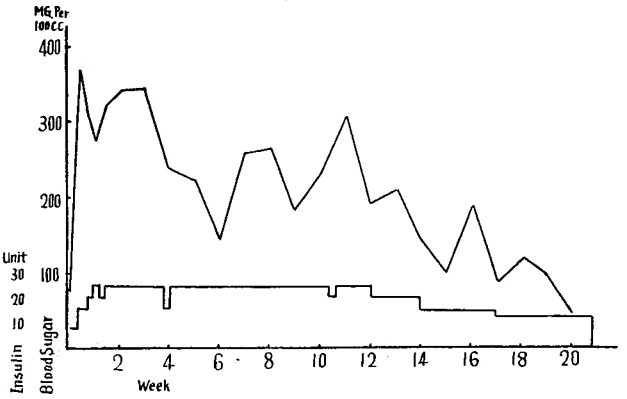


Fig. 7 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Totally Depancreatized Man. (Case 2)

Case 3, A man aged 59. At the time he was admitted to our Hospital, considerably severe dysfunction of the liver was found, and also after operation it did not readily recover, and therefore his appetite was poor for a long time. The blood sugar level in this period when he was receiving daily 15 units of protamin zinc insulin, sometimes became so high (Fig. 8), that it got up beyond 400 mg. per 100 cc, and sometimes it became as low as 54 mg. per 100 cc or 11 mg. per 100 cc, and hypoglycemic signs often appeared. The blood sugar level in this case was thus very unstable. Then we tried to control the blood sugar level by using regular insulin twice a day, instead of administering protamin zinc insulin once a day, and the daily dose was also reduced to 5 units. Several weeks after this method was adopted, the function of the liver began to recover gradually and his appetite became better, accordingly the daily insulin requirement was increased gradually. Thereafter he kept the satisfactory condition, but from the 9 th post-operative month the function of the liver aggravated again and a marked decrease in appetite reappeared, consequently gradual reduction of the insulin dose became necessary. He died 344 days after operation from liver cirrhosis.

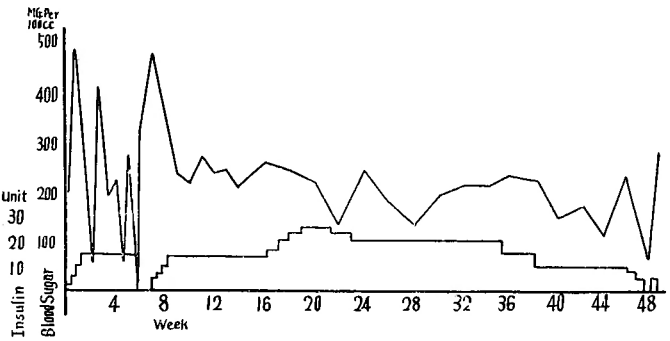


Fig. 8 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Totally Depancreatized Man. (Case 3)

Both in cases 4 and 5, the appetite was disturbed as the result of complications such as recurrence of cancer or peritonitis, therefore it was necessary to reduce the insulin dose and finally they died 3 months and 1 month respectively after operations.

As stated above, in totally pancreatectomized men, if their appetite was disturbed

as a result of some complications following operation, reduction of the insulin dose was necessitated, but on the other hand in the patients with good appetite and without any complication there was no need of reduction. These observations in men were somewhat different from those in dogs, for there were some dogs in which reduction of the insulin dose were necessary in spite of their sound appetite.

(II) PARTIALLY PANCREATECTOMIZED DOGS

It is generally accepted that severe diabetes would take place when the pancreas was totally removed. To which extent can the pancreas be resected without causing diabetes ?

According to ALLEN, glycosuria occurred in dogs when the pancreas was resected over four fifths. DRAGSTEDT stated that glycosuria did not occur when about 10 per cent of the pancreas remained as far as it was connected with the bowel through pancreatic ducts. According to IZUKA, however, because the functional deficiency due to the lack of the pancreas would probably be compensated with some other organs, total pancreatectomy without resulting in glycosuria might be possible if the removal was carried out in several stages.

I prepared a series of dogs in which resection of the pancreas was performed to various extents, and the correlation between the extent of resection and the resulting glycosuria was studied. And at the same time, changes in the blood sugar level and the insulin dose required after subtotal pancreatectomy, which was performed in two stages with an interval of 2 months, were also followed up.

There was no change in the blood sugar level when the caudal half of the pancreas was removed. Resection of about two thirds or three fourths of the pancreas produced transient elevation of the blood sugar level soon after operation, but it returned to the pre-operative level after about one week without receiving insulin.

Observations in two dogs in which about nine tenths of the pancreas was resected and only one tenth of the head of the pancreas remained in the neighborhood of the opening of the main pancreatic duct, revealed that the blood sugar level was slightly elevated during one week post-operatively in both cases, then dropped to the pre-operative level without insulin administration. One of them died as the result of dilatation of the biliary duct and jejunal ulcer 4 weeks after operation, maintaining the normal level of blood sugar, and in another one, the amount of blood sugar began to increase from the 11th post-operative week, and the insulin admi-

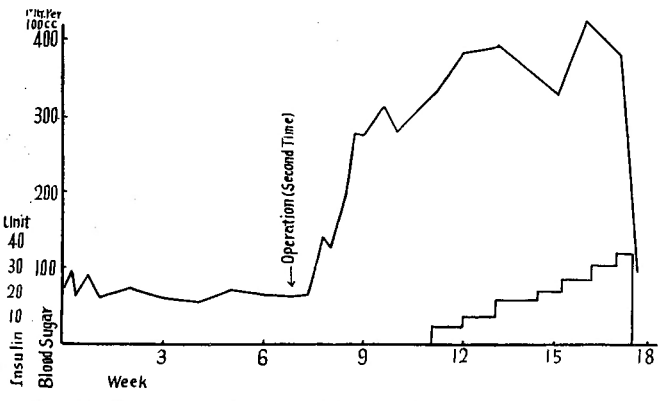


Fig. 9 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Partial-Pancreatectomized Dog. (No. 9)

nistration became necessary.

In the dogs, whose pancreas had been resected in two thirds or three fourths by the first operation, the remaining portion of the pancreas was once more resected 2 months later in one half or two thirds respectively, thus leaving only about 10 per cent of the original size of the pancreas. Results obtained in these cases are shown in Fig. 9 and 10 respectively.

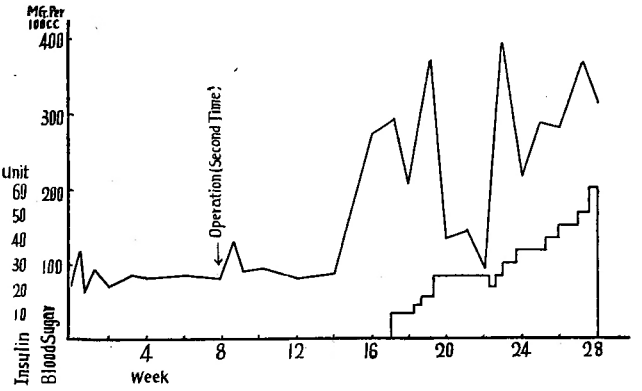


Fig. 10 Changes of the Blood Sugar Level and the Dose of Insulin Required in a Partial-Pancreatectomized Dog. (No. 7)

During a certain period after the second operation, the blood sugar level did not increase so much but later elevated gradually showing some fluctuations, and insulin had to be administered after 4 weeks in one case and after 9 weeks in the other. Thereafter, the daily insulin requirement increased gradually to reach such a large amount as 35 and 60 units, and these doses were much larger than those for totally depancreatized dogs. And they died 28 and 18 weeks after the first operation respectively. But their appetite was very good until they died, and the feces were much nearer to normal than those of totally depancreatized dogs.

(III) PANCREATIC DUCT LIGATION DOGS

Changes of the blood sugar level were examined in the dogs, whose pancreas was freed from the duodenal wall and then the duodenum was totally removed in order to make sure the effect of the ligation of pancreatic ducts. The blood sugar level was in normal range, and no particular change was observed.

(IV) INSULIN TEST

When the insulin test was performed in normal dogs in the state of fasting, the blood sugar dropped to its lowest level 30 to 60 minutes after injection and then it ascended rapidly to reach the initial level before injection after 2 hours, this level continuing long thereafter.

The same test was carried out in totally pancreatectomized dogs. The results are illustrated in Fig. 11. The time required for reaching the lowest level was always longer than that in normal dogs, and the shape of the curves was quite different from that of the latter. There were two kinds of curves. a) The blood sugar level descended steadily on one way after insulin injection. b) After the drop, the blood sugar level ascended again gradually, but not to the initial level before injection. The curve of a) type was almost always obtained in the dogs in which a considerably long time elapsed after operation and the weakness was severe. The curve of b) type, on the contrary, was usually seen in the dogs, in

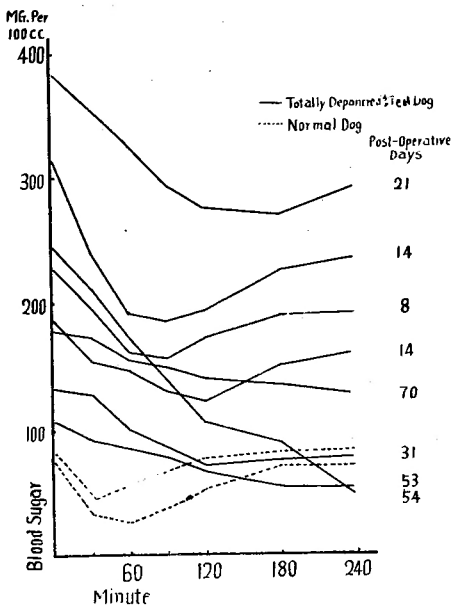


Fig. 11 Changes of the Blood Sugar Level after Insulin Injection in Totally Depancreatized Dogs.
(Dose of Insulin : 0.1~0.3 U. per KG. Intrevenously Injected)

Tadle 3 Assimilation Index Obtained from Totally Depancreatized Dogs.

Assimilation Index	
Normal Dogs	Totally Depancreatized Dogs
0.56	0.16
0.65	0.45
0.87	0.32
1.06	0.11
1.30	0.37
1.25	0.21
1.10	0.32
1.55	0.28

Table 4 Assimilation Index Obtained from Totally Depancreatized Dogs.

Dog No.	Assimilation Index	
	Frst Time	Second Time
18	0.501	0.378
77	0.162	0.399
82	0.283	0.212
M 1	0.503	0.455
M 3	0.450	0.352
M 4	0.103	0.108
M 7	0.311	0.420

which the post-operative course was short and the body weight was not reduced so markedly.

If the assimilation index, which indicates insulin sensitivity, is calculated from these curves, as Table 3 shows, it is always lower in totally depancreatized dogs than in normal. Thus it would be surmised that totally depancreatized animals are insensible to insulin. The assimilation indices calculated from the insulin tests performed twice with an interval of 2 to 5 weeks are shown in Table 4. In 4 dogs out of 7, the index at the second test was lower than that at the first, but in the remaining 3 dogs the result was reverse. Thus, a constant change in the insulin sensitivity of depancreatized dogs in the course of time after operation was not demonstrated.

In the insulin test in fasting men, using 10 units of insulin (subcutaneous injection), the blood sugar level reached the lowest level 60 minutes after injection, and then ascending gradually, it returned in 4 hours to the level before injection. Throughout the test no hypoglycemic sign did appear.

The same tests were carried out for 3 times during the post-operative course in a patient who had undergone total pancreatectomy. As shown in Fig. 12, almost similar curves were obtained at each time of the tests, and they differed greatly from those in normal men. That is, the blood sugar level descended steadily on

one way for a long time, though the tempo of dropping was very slow. The recovery in the blood sugar level did not occur readily and sometimes hypoglycemic signs were observed. Calculating the assimilation index from these curves, as Table 5 shows, it was always lower than in normal men. And it was revealed that these patients had become insensible to insulin in the same way as in dogs.

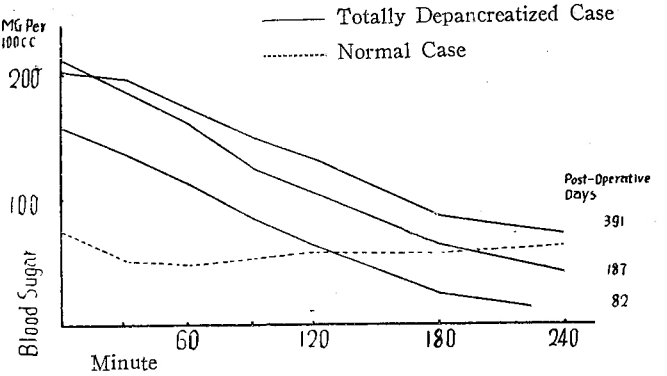


Fig. 12 Changes of the Blood Sugar Level after Insulin Injection in a Totally Depancreatized Man. (Insulin Injection : 10 U. Subcutaneously)

Table 5 Assimilation Index Obtained from a Totally Depancreatized Man.

	Post-Operative Days	Assimilation Index
Totally Depancreatized Human Case	82	0.40
	187	0.38
	391	0.27
Normal Case	—	0.55

DISCUSSION

DRAGSTEDT pointed out the fact that the insulin requirement in totally depancreatized dogs was reduced markedly with the lapse of time after operation, due to the fatty liver caused by the lack of the pancreatic hormone "lipocaic", which he had assumed to prevent the development of the fatty liver.

In my experiments, however, a marked reduction in the insulin requirement was necessary in only 4 of 23 totally depancreatized dogs surviving more than 4 weeks after operation, and moreover only in 1 out of these 4 dogs the definite fatty liver was found at autopsy. Accordingly I can not consent to DRAGSTEDT in that he explained the marked reduction of the insulin requirement exclusively from the standpoint of the fatty liver.

It is worthy of note that in about one half of my experimental dogs, some reduction of the insulin dose was necessary with the lapse of time post-operatively, in spite of their good appetite and the absence of the fatty liver, while on the other hand, in totally depancreatized men, the insulin dose had to be reduced only in the patients with impaired appetite.

How should we explain the difference between dogs and men ?

HAMANO in our Clinic observed that the digestive and absorptive functions of the gastrointestinal tract were remarkably disturbed after total pancreatectomy, and that the disturbances were much severer in dogs than in men. Thus it may be reasonable to assume that totally depancreatized dogs are apt to fall into chronic inanition in spite of their good appetite, necessitating the gradual reduction of the dose of insulin administered, while depancreatized men are usually in fairly good nutrition except for the patients whose appetite is severely impaired.

All dogs but one in which the insulin dose was not reduced throughout or for the most part of the post-operative course following total pancreatectomy, maintained comparatively good digestion and absorption as the result of receiving pancreatin and methionine.

The daily amount of insulin administered in totally depancreatized dogs at the time when their appetite did recover, was 30 units in maximum and 8 units in minimum, and in the majority 12 to 25 units. In the case of total pancreatectomized patients, it was about 25 units. These amounts of insulin both in dogs and patients are, as already has been pointed out by BRUNSCHWIG, THOROGOOD and ZIMMERMANN, SPRAGUE, GASTON, PRIESTLEY et al, and FALLIS et al, fairly less than those required in alloxanized dogs or clinical diabetics. Therefore, it should be concluded that diabetic signs appearing in totally depancreatized dogs as well as men whose β-cells of Langerhans islets have been completely lost, are slighter than those in alloxanized dogs or clinical diabetics in which β-cells of the pancreas are stillremaining, though few.

In this connection a hypothesis has been proposed by THOROGOOD and ZIMMERMANN that the second pancreatic hormone, which increases sugar in the blood and urine but prevents the development of ketosis and diabetic coma, would probably be secreted from α-cells of Langerhans islets. They stated also that this hormone might be the same substance with lipocaic assumed by DRAGSTEDT et al. FALLIS and SZILLAGYI postulated also the second pancreatic hormone acting antagonistically to insulin, through their experiences in totally depancreatized patients. Against this, SPRAGUE stated that one should be careful to assume the existence of such second hormone only from the fact that the amount of the insulin requirement of depancreatized patients was smaller than that of clinical diabetics, and called attention to the fact that their nutritional conditions had become very worse as the result of the absence of the external pancreatic secretion.

It has been noticed that insulin had an effect to increase blood sugar for a few minutes immediately after injection prior to the decrease in the next stage, and it has been investigated what kind of mechanism may concern with this phenomenon. Regarding this, HEARD et al obtained an extract from protein contained in insulin which accelerated the glycogenolytic action in the liver and increased blood sugar. SUTHERLAND and DE DUVE also extracted from the pancreas a glycogenolytic factor working directly on the liver, and they observed that an extract obtained from the pancreas of alloxan-diabetic dogs increased the blood sugar level of rabbits. GAEDE also obtained an extract from the pancreas which produced hyperglycemia and he named it "glucagon".

On the other hand, HASEGAWA in our Clinic, examined histologically the anterior pituitary of totally depancreatized dogs, and found a marked reduction in number of chromophil cells. And AOKI, one of my coworkers, pointed out the reduction of fat tissue in the adrenal cortex. Thus it is probable that there is the hypofunction of the anterior pituitary and adrenal cortex.

The fact that the insulin requirement after total pancreatectomy both in dogs

and men is unexpectedly small, might probably be due (1) to the hypofunction of the pituitary-adrenocortical system which works antagonistically to insulin, and (2) to the lowering of the digestive and absorptive function of the intestine. Of course the possibility of the vanishing of "glucagon", the second pancreatic hormone, which is considered to elevate blood sugar antagonistically to insulin, if really present, is not neglegible.

The increase in the amount of blood acetone body after total pancreatectomy was not so marked in spite of the considerably high level of blood sugar (under the administration of insulin). This result corresponds to the experiences of FALLIS, THOROGOOD, and so on.

Removal of nine tenths of the pancreas of dogs, produced diabetes, corresponding approximately to the reports of ALLEN, DRAGSTEDT, YOSHIOKA and others. However, the mode of its appearance was not so simple as the statement of YOSHIOKA that the blood sugar level ascended steadily on one way, and the animals used to die shortly after resection of the pancreas.

The fact that the insulin requirement in two dogs in which subtotal pancreatectomy was carried out in two stages was much larger than that in totally depancreatized dogs, might be due to the better digestion and absorption in those dogs than in totally depancreatized animals, as HAMANO reported, because subtotally pancreatectomized animals possibly retain some external secretion of the pancreas.

From the observations that the insulin requirement after total pancreatectomy was unexpectedly small, and sometimes hypoglycemic symptoms did occur, it has been generally believed that the sensitivity to insulin increases following this type of operation. The fact is, however, that in the insulin test, the tempo of decrease of the blood sugar after insulin injection is slower in pancreatectomized men, and the assimilation index shows the insensibility of these patients to insulin. For the explanation of this fact, it should be considered that the function of the pituitary-adrenocortical system which elevates the blood sugar antagonistically to insulin, would more or less predominate in the case of total pancreatectomy, although this system tends to become hypoactive after this operation.

The results of my study that (1) in some patients of total pancreatectomy the blood sugar level dropped continuously at the time of insulin test, while (2) in some others it ascended again gradually after having dropped to the bottom, though not so high as before injection, are probably be explained by the more intensely lowered nutrition in the patients of (1) due to the disturbed digestion and absorption and by the severer hypofunction of the pituitary-adrenocortical system in the same patients.

CONCLUSIONS

In the present experiments, the blood sugar level and the dose of insulin required after operations on the pancreas, especially after total pancreatectomy, have been examined during the post-operative course, and also the insulin test has been carried out in totally depancreatized dogs and men. Conclusions are as follows.

(1) The dose of insulin required after total pancreatectomy was smaller than that in alloxan-diabetic dogs or clinical diabetics.

(2) The marked reduction of the insulin requirement was noticed in only 4 of 23 depancreatized dogs surviving more than 4 weeks after operation, and moreover in only 1 of these 4 dogs the development of the definite fatty liver was confirmed at autopsy.

(3) In totally pancreatectomized men, only those cases, whose appetite remarkably decreased in consequence of some complications, had to receive the reduced dose of insulin with the lapse of time, but on the other hand, the patients, whose appetite was good and free from any complication, had no need of reducing insulin.

(4) The gradual reduction of the insulin requirement observed in totally pancreatectomized dogs may be accounted for, not merely by the development of the fatty liver but chiefly by the marked disturbance of digestion and absorption after operation. In totally depancreatized men the gradual reduction of the dose of insulin was not so frequently needed as in dogs. This difference between dogs and men may be explained with the maintainance of the better digestion and absorption in men after operation.

(5) It has been believed that the sensitivity to insulin tends to increase after total pancreatectomy. As a matter of fact, however, the tempo of decrease of the blood sugar level after insulin injection (insulin test) is slow, and the assimilation index shows that the individuals are rather insensible to insulin.

(6) The increase in the amount of blood acetone body after total pancreatectomy was not so marked, in spite of the considerably high level of blood sugar (under the administration of insulin).

(7) In dogs diabetes appeared by the removal of caudal nine tenths of the entire pancreas. However, the blood sugar level of these animals did not always ascend on one way after operation.

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和文抄録

膵全剔後の血糖値とインシュリン投与量，特にインシュリン感性に就いて

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従来から，膵全剔犬及び人体は，インシュリンに対し感受性が増強しており，屢々低血糖症状を呈すると言われて来た．Dragstedt は，膵全剔犬に見られるかかる現象は，抗脂肝性ホルモン（彼の謂う）"Lipocaic" の欠除の結果惹起される脂肪肝の特徴であると述べている．

しかし乍ら，従来から，膵全剔人体例に於いては脂肪肝は殆ど発見されておらず，且つ当教室の青木は，膵全剔犬に於いても脂肪肝は殆んど発見されないと述べている．

そこで，我々は，膵全剔犬及び人体のインシュリン感受性の問題を検討する為に，術後の血糖値とインシュリン投与量の変動を追求し，併せてインシュリン・テストを施行した．尚，ケトン症の発生を予防するために，術後経過を追つて血中アセトン体値を測定した．

膵全剔後4週間以上生存した犬23頭の中で Dragstedt が報告したように，術後時日の経過と共に著明にインシュリン投与量を減少させねばならなかつた例は

4頭のみであつた.

しかも，此の4頭の中で剖検によつて，脂肪肝が認められたのは，1頭に過ぎなかつた.

膵全剔人体例では，術後合併症が併発し，食思不振に陥つた例のみが，術後時日の経過と共に著明にインシュリン投与量を減少せしめねばならなかつたが，合併症の併発しない例では何らその必要を認めなかつた.

従つて，膵全剔犬並に人体例に見られたインシュリン投与量漸減の事実は，脂肪肝の発生にのみその原因を求めるよりも，むしろ，教室浜野の実験が示すように，術後の消化吸収能力の著明な低下に重点を置く可きであり，膵全剔犬は術後食思旺盛でも，消化吸収障碍の為に一種の慢性飢餓状態に陥つて居り，その影響が加算される結果インシュリン投与量の漸減を必要とし，膵全剔人体例では犬に較べその消化吸収能力が比較的良好なために，食思の障碍された例のみその必要を認めるようになつたものと理解される.

従来膵全剔後にインシュリン投与量が時日の経過と共に著明に減少すると云われたことから，インシュリンに対し感受性が増強すると考えられて来たが，実際は，同化率が示すように，インシュリン注射後の血糖の下降速度は反つて緩慢となり，インシュリンに対し鈍感になつていることが判明した.

膵全剔犬及び人体の1日のインシュリン投与量は，重症のアロキサン糖尿犬，内科的糖尿病患者のそれよりも少量であつた．その理由としては，インシュリンに拮抗し，血糖を上昇させる第2の膵臓ホルモン"Glucagon"も膵全剔の際同時に，除去されるからであるとも云えようが，一部は，インシュリンに拮抗的に作用する脳下垂体前葉一副腎皮質機能の低下更に，腸管の消化吸収能力の低下等に由来するものと考えたい.

膵全剔後の血中アセトン体値は，インシュリンさえ投与しておれば左程高値を示さなかつた.