CALCIUM METABOLISM AFTER TOTAL PANCREATECTOMY

by

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INTRODUCTION

There have been numerous investigations on carbohydrate metabolism, especially with regard to the role of insulin, and on fat metabolism, principally on the problem of fatty liver and the ability of digestion, etc., after total pancreatectomy.

However, there has been almost no research on the metabolism of inorganic substances. We can find only one report, by FALLIS et al, concerning the absorption and the discharge of calcium in one totally pancreatectomized patient.

It has been recognized by many investigators that there are marked disturbances in the digestion of fat and protein after total pancreatectomy.

It is probable that considerable changes in the metabolism of calcium must take place, due to the post-operative metabolic changes of fat digestion. Moreover, one patient of our series revealed symptoms of tetany eight months after the operation and, at the same time, showed a marked decrease in serum calcium. But this patient recovered soon after an adequate intake of calcium. Therefore I think it is necessary to investigate the changes in calcium metabolism after total pancreatectomy.

I performed examinations on the digestion of calcium, serum calcium, bone changes, the parathyroid glands, etc.

The results may be stated as follows:

ABSORPTION AND EXCRETION OF CALCIUM

The small intestines, especially the duodenum, are most important sites for the absorption of calcium salts, and the liver, the pancreas and the epithelium of the bowels excrete calcium into the feces, and the kidney into the urine.

In normal adults, the amount of calcium absorbed and excreted is the same, so that the amount of calcium is kept in balance.

Conditions which hinder the solubility of calcium salts in the intestinal tract prevent its absorption. Thus the concentration of hydrogen ions in the upper portion of the small intestines, other substances in the foods, such as phosphorus, magnesium, fat etc., play an important role in the assimilation of calcium.

Vitamin D may also participate in calcium absorption and excretion in two ways, one in relation to the combination of phosphorus in the tissues, and the other in the deposition of calcium phosphate to form bone. Besides, absorption, in

large part, depends on the time during which the food remains in the intestines.

I performed the following experiments to study calcium balance after total pancreatectomy.

(A) METHODS OF EXPERIMENT

In this experiment adult dogs of both sexes weighing about 10 kg were used. After total pancreatectomy we controlled the blood sugar level at about 200 mg per 100 cc by insulin administration. Several weeks after the operation I fed them a test diet containing a definite dose of calcium as shown in table 1, and then collected the feces for three or four days. Neither diarrhea nor constipation occurred after the dogs had been accustomed to the test-diet. The collected feces were desiccated and then crushed into powder. The daily output of calcium in the feces was calculated by McCRUDDEN's method.

I also studied calcium balance in a patient, who had undergone total pancreatectomy two years before and was still living a healthy life.

Table 1 Test-diet (Dog) Containing 800 Calorie and 840 mg of Calcium

Rice	200g
Soup	200cc
Sugar	25g
Methionin	2g
Vitamin B_1	0.5g
Vitamin C	5g
Pancreatin	5g
Ca-Phosphate	2g

Table 2 Test-Diet (Man) Containing 2500 Calorie and 1060 mg of Calcuim

Rice	300g
Bread	200g
Potato	300g
Soup	300g
Egg	3
Butter	50g
Orange juice	300cc
Tea	300cc
Ca-Phosphate	7g
Pancreatin	5g

SCHERMAN stated that the adult man needs a minimum dose of 0.45 g calcium per day to maintain calcium balance, and the proper amount is 0.68 g which is an increase of 50 per cent. But we would like to point out that the advisable dose should be 1 g a day in consideration of some digestive disturbances. Therefore, I gave the test-diet which contained the standard quantity of calcium as shown in table 2, and then collected the feces and determined the calcium out-put. In addition, I collected the total urine during twenty-four hours, and calculated the urinary calcium out-put by McCRUDDEN's method.

(B) RESULTS

As a control we used an normal adult dog weighing about 10 kg. Tables 3 and 4 show the absorption and excretion ratio. As shown in table 3, the amount of feces of the totally pancreatectomized dogs is very large, since in totally pancreatectomized dogs digestive ability was greatly disturbed in spite of pancreatin administration, as has been recognized by COFFEY, SELLE and PRIESTLEY, and a large quantity of poorly digested diet is excreted in the feces.

Table 3 Daily out-put of calcium (Dog)

After Operation	Daily out-put of feces	Daily out-put of Calcium	Calcium ba lance
6week	55g	715mg	175mg
7week	64g	3200mg	-2360mg
7week	52g	1040mg	- 200mg
8week	65g	910mg	70mg
Control	20g	500mg	340mg

Table 4 Daily out-put of calcium (Man)

Total Ca intake	1060mg
Urine Ca	168mg
Stool Ca	950mg
Total out-put	1118mg
Ca balance	-58mg

Generally speaking, after total pancreatectomy postoperative metabolic changes are milder in men than in dogs. In the digestion of calcium also, as shown in table 4, it was found that the metabolic balance in man was not so much disturbed as in the dog.

In the dog, the collection of urine was so difficult that we could not determine the daily out-put of calcium in the urine. If we could estimate it and add it to the fecal excretion, all the cases operated on would show a negative calcium balance.

I gave the diet mixed with carbon-powder and found that the totally pancreatectomized dog excreted black stool within five to six hours after ingestion. This fact confirms the previously mentioned statement that the passage of the intestinal contents is so rapid that calcium and other nutriments cannot be absorbed sufficiently.

Moreover the digestive disorder of fat disturbs calcium digestion because of the formation of calcium-soap, as well as causing lowering of the absorption of fat soluble vitamins, especially vitamin D resulting in vitamin D deficiency which causes further lowering of calcium absorption and an increase of calcium excretion from the bowel.

SERUM CALCIUM

In normal adults, the serum calcium is between 9 mg and 11.5 mg per 100cc, in normal adult dogs, between 9.5 mg and 12 mg per 100cc. These values are stationary and vary only in a restricted range among individuals and with seasons. Calcium is present in plasma in several forms. About half of the total serum calcium is bound to proteins and is not diffusible; the greater portion of the remaining half exists in the ionized state, while the rest is present in some complex combination with other substances which are not yet identified. The latter two portions are diffusible, passing freely through semipermeable membranes. The concentration of these diffusible calcium are of great importance, both physiologically and clinically, since bone formation, neuro-muscular irritability, blood coagulation, etc. are influenced mostly by them.

In adults, the diffusible serum calcium level is between 4.3 mg and 5.2 mg per 100 cc and it is regulated by the parathyroid glands. A decrease in the diffusible serum calcium stimulates the parathyroid glands to secrete more hormone. Hypersecretion of the parathyroid glands stimulates directly the secretion of alkaline phosphatase by the osteoblasts and the bone calcium makes a change into a soluble

one. Consequently the mobilization of bone calcium into the blood stream takes place, and thus the serum calcium level makes an increase.

Hypofunction of the parathyroid glands causes a decrease in diffusible calcium resulting in tetany. As has been previously mentioned, the serum protein level also has an intimate interrelationship with the serum calcium level, namely as follows;

$$\text{PROTEIN}-\text{CALCIUM} \rightleftharpoons \text{PROTEIN}^{--} + Ca^{++}$$

The acid-base balance also influences the serum calcium level through its effect on dissociation of serum protein and the mobilization of bone calcium. The serum calcium level increases in conditions of acidosis, and decreases in alkalosis.

In these ways the value of serum calcium is influenced by many various factors.

(A) METHODS OF EXPERIMENT

I determined the serum calcium value by SOBEL's method, using fasting blood taken in the early morning, in order to avoid fluctuation in the blood calcium level after meals.

I used adult dogs about 10 kg and determined their serum calcium level before total pancreatectomy and then every week after the operation controlling their blood sugar level at about 200 mg per 100cc by insulin administration. I determined also the serum calcium in three totally pancreatectomized men.

(B) RESULTS

The results of the experiment are shown in Fig. 1 and Fig. 2.

The changes are almost within the normal range but some decrease below the normal range is recognized in a few cases. But as mentioned previously, the serum calcium consists of a non-diffusible fraction and a diffusible, and the latter is of much greater importance, both physiologically and clinically. I determined the serum protein level simultaneously and calculated the amount of diffusible

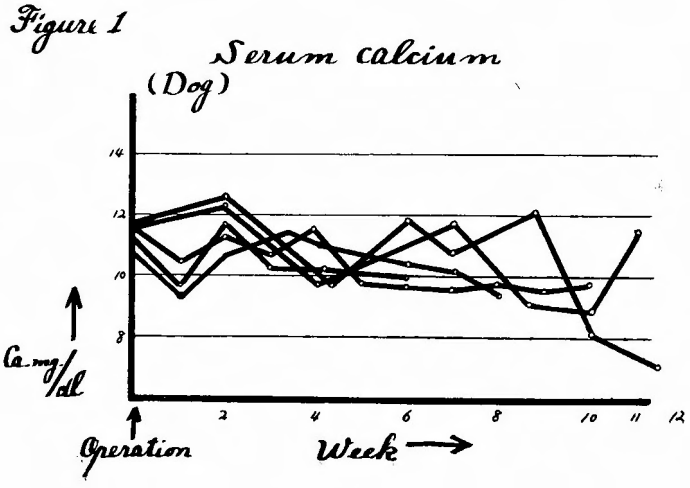
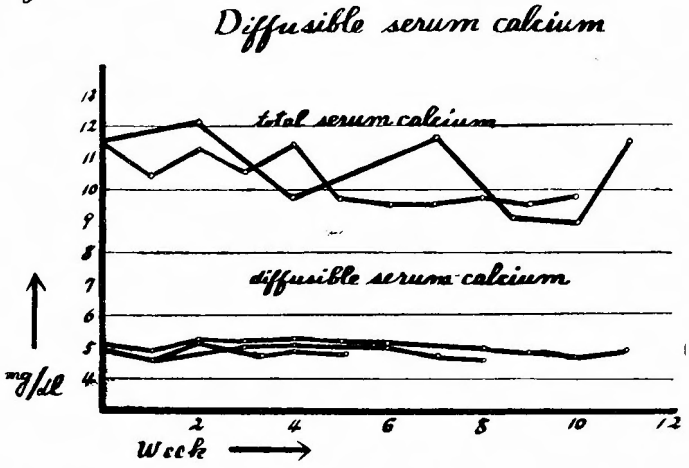


Figure 2



calcium from the graph of McLean and Hasting (p.899).

It was found the diffusible calcium levels were within the normal range and there were no changes as shown in Fig. 2 in any of the cases.

This fact demonstrates that the changes and the decrease of the blood calcium level after total pancreatectomy are due to the decreased non-diffusible calcium, which is due to the hypoproteinemia shown by the N negative balance resulting from the digestive disorder.

It is generally recognized that patients with diabetes mellitus may develop acidosis, but during my experiment I could not find any symptoms of acidosis, or any increase of acetone in the blood. Fallis has also stated the same findings in his clinical report.

Accordingly, we may presume that changes in the serum calcium level due to disturbances of acid-base balance following total pancreatectomy may be put out of consideration.

Eventually, because the diffusible calcium of serum which probably is physiologically active is regulated by the parathyroid glands, whenever the parathyroid function is normal, the diffusible calcium level will be kept within the normal range.

However, we should not look over the fact that one patient developed tetany and that the amount of the serum diffusible calcium in that patient was decreased as shown in tables 5 and 6.

Table 5 Serum calcium mg/dl

after Operation / Patient	1mon.	2	6	1year	2	3
Case 1					10	10
Case 2				10.2	10	
Case 3	8.8	7.3	8.6	7.8		

Table 6 Diffusible serum calcium
(The last case in table 5)

Total serum calcium	7.8mg/dl
Serum protein	4.8g/dl
Diffusible serum calcium	4.1mg/dl

CHANGES IN BONE

Bone consists of inorganic substances and an organic matrix, and the inorganic substances which are deposited in the organic matrix are almost all in the form of calcium phosphate.

Calcium which is absorbed from the upper small intestines, enters the blood stream, and part of it supplements the serum calcium and the remaining larger part is deposited in the bone.

At the same time, calcium phosphate in the bone dissolves continuously into the blood stream by the activity of the osteoclasts. Thus bone is continuously being renewed. But after total pancreatectomy some metabolic changes may take place such as disturbance of absorption, and increased excretion of calcium and deprivation of vitamin D which in turn may probably cause some changes in bone.

(A) METHODS OF EXPERIMENT

I used adult dogs as did in the preceding experiments and controlled the blood sugar level at about 200 mg per 100cc by insulin administration after total pancreatectomy. I extirpated a rib from the dogs during three to twelve weeks after the operation.

I calculated the calcium contents in the bone by McCRUDDEN'S method. In all the cases, I used the cortex of the rib in order to avoid structural differences.

In addition, I made histological specimens from the decalcified rib and dyed them with hematoxylin-eosin.

(B) RESULTS

One third to one half of the bone calcium was exhausted three to twelve weeks after the operation as shown in table 7. This is partly because of the disturbed absorption of calcium and mostly because of the disturbance of calcium deposition in bone due to vitamin D deficiency caused by disturbance of its absorption. The reason for maintenance of the serum calcium level within the normal range despite the excretion of a large amount of calcium in the feces may well be explained by the consumption of bone calcium. Besides, the histological preparation showed osteoporosis. As shown in the photograph, there is marked restriction of ossification in the periosteum and marrow. Moreover, Howships-lacunae-like defects of the bone were found. The bone shaft became thin and the tissue surrounding Havels' canals stained only slightly. But in clinical cases no changes in the X-ray findings were recognizable.

Table 7 Bone Calcium

after Operation	Ca Contain	Consumption
3 weeks	11%	45%
4 weeks	13%	35%
5 weeks	16%	20%
12 weeks	11%	45%
12 weeks	14%	30%
12 weeks	14%	30%
Control	20%	
Control	20%	

CHANGES IN PARATHYROID GLANDS

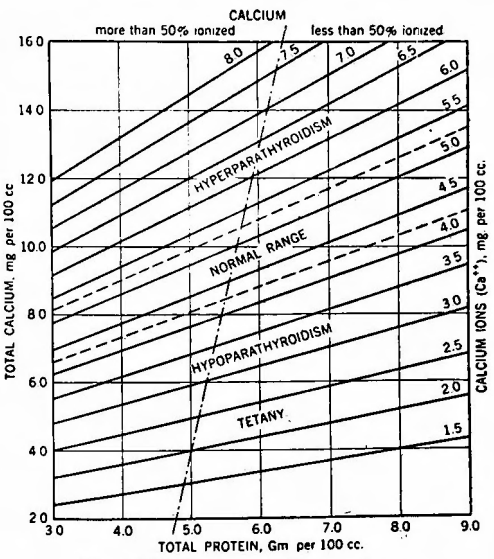
SHIFF pointed out in 1884 that dogs and cats developed tetany when the thyroid glands were extirpated, and VASSEL explained that tetany was due to the extirpation of the parathyroid glands. After that, ERDHEIM reported the results of his fine research, and then, COLLIP in 1925 independently prepared an active parathyroid extract. The relationship between the parathyroid gland and the other glands still remains unknown. In dogs and in human children before the age of 10 years, only chief cells are present. The cytoplasm of these cells is clear, containing a large rounded nucleus. These are the secreting cells. After the tenth year the oxyphil cells begin to appear. They are larger than the chief cells and have abundant eosin-staining granules in their cytoplasm.

Parathyroid hormone influences calcium and phosphorus metabolism. Deprivation of the parathyroid hormone causes a decrease of the diffusible serum calcium and an increase of the serum inorganic phosphorus and occasionally causes tetany. An excess of the hormone causes an increase of the diffusible serum calcium level and a decrease of the inorganic phosphorus level and an increase of the out-put of the urinary calcium and phosphorus, thus leading to decalcification of the bone. The low level of blood calcium ions stimulate the parathyroids to work.

I performed the following experiments in order to investigate the altered attitudes of the parathyroid glands after total pancreatectomy.

As already mentioned above I recognized the fact that after total pancreatectomy there was a negative calcium balance accompanied by vitamin D deficiency which might have resulted from the absence of the external secretion of the pancreas. Moreover, I had an idea that the absence of the internal secretion of the pancreas might influence the parathyroid glands.

(A) METHODS OF EXPERIMENT



(from McLEAN and HASTING)

(i) MORPHOLOGICAL EXAMINATION

I killed dogs by blood-letting three to twelve weeks after total pancreatectomy, and then extirpated the parathyroid glands.

I also extirpated the parathyroid glands from one patient who had survived two years after total pancreatectomy. The extirpated glands were stained with the HEIDENHEIN'S modification of AZAN'S staining method and with hematoxylin-eosin.

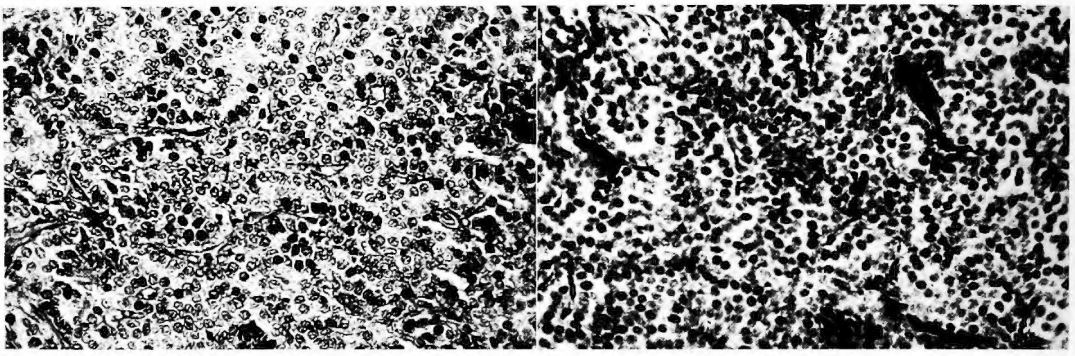
(ii) OXALATE TOLERANCE TEST

When a large quantity of sodium oxalate is injected in the dog, the serum calcium level decreases markedly because the calcium ions in the blood stream precipitate as calcium oxalate. But the decreased serum calcium level will reestablish itself within the normal range by the action of parathyroid hormone within five to six hours after the injection of sodium oxalate.

As PATT mentioned, the recovering curve of the serum calcium level reveals the activity of the parathyroid glands.

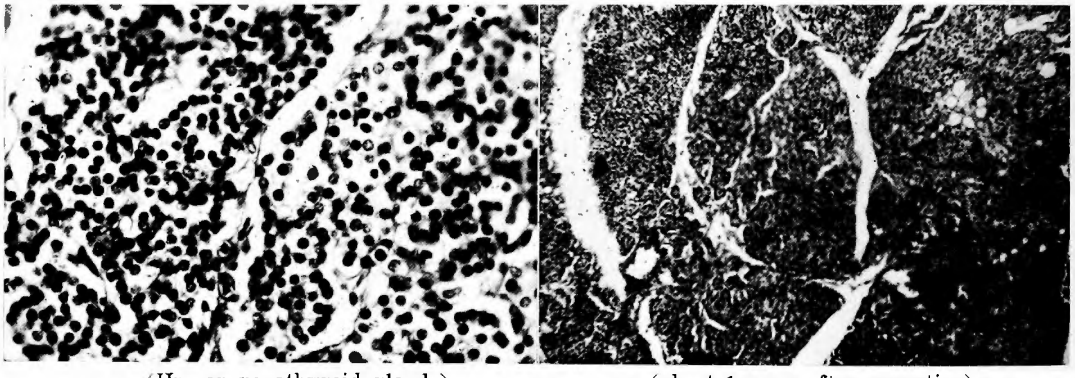
I injected sodium oxalate intravenously, 40 mg per kg, in totally pancreatec-

Photo. 1 Parathyroid gland Photo. 2



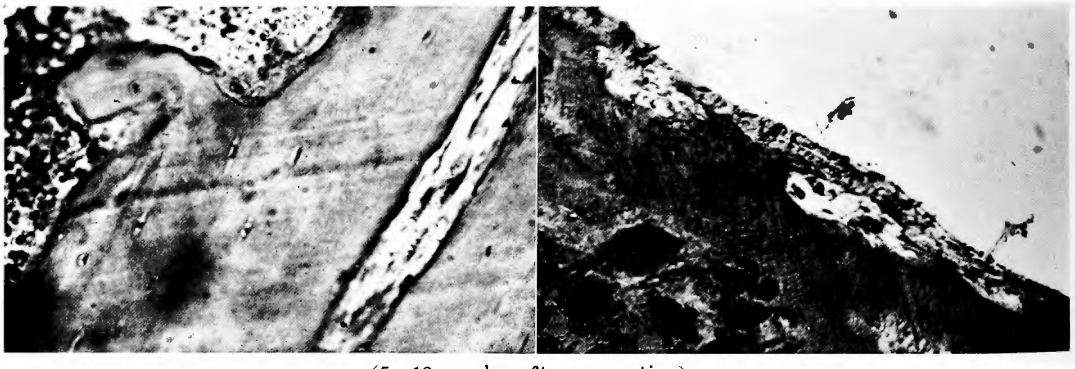
(7Weeks after operation) (7months after subtotal pankreatectomy)

Photo. 3 Photo. 4



(Human parathyroid gland) (about 1 year after operation)

Photo. 5 Bone Photo. 6



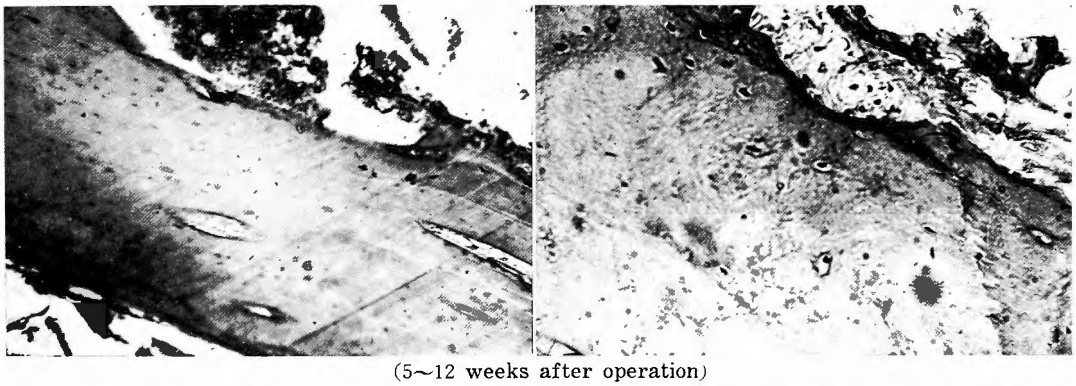
(5～12 weeks after operation)

tomized dogs and determined the serum calcium values every hour during five or six hours after the injection.

(iii) SERUM ALKALINE PHOSPHATASE

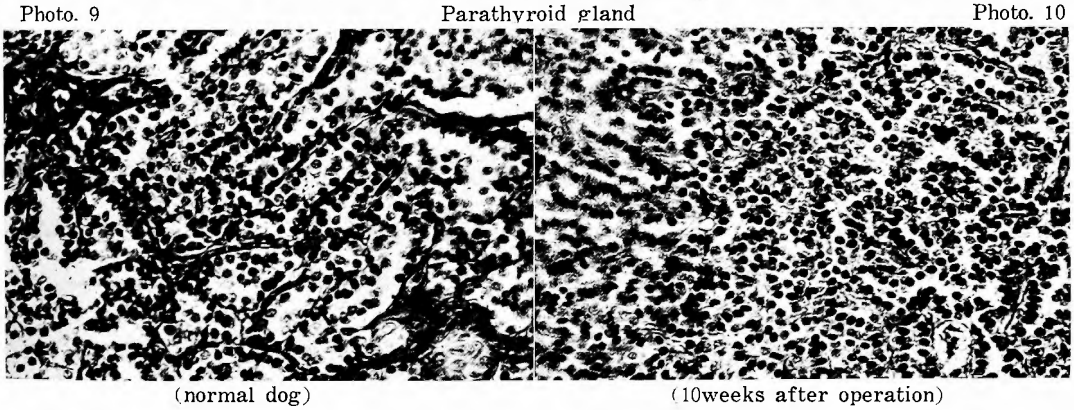
Normally 2 to 4 BODANSKY units per 100cc of alkaline serum phosphatase is found in the blood. An alteration of the amount of serum phosphatase is deemed to be an index for the activity of the parathyroid glands. The parathyroid hormone affects the osteoblasts and stimulates secretion of alkaline phosphatase. Accordingly hyperfunction of the parathyroid glands results in an increase of serum

Photo. 7 Bone Photo. 8



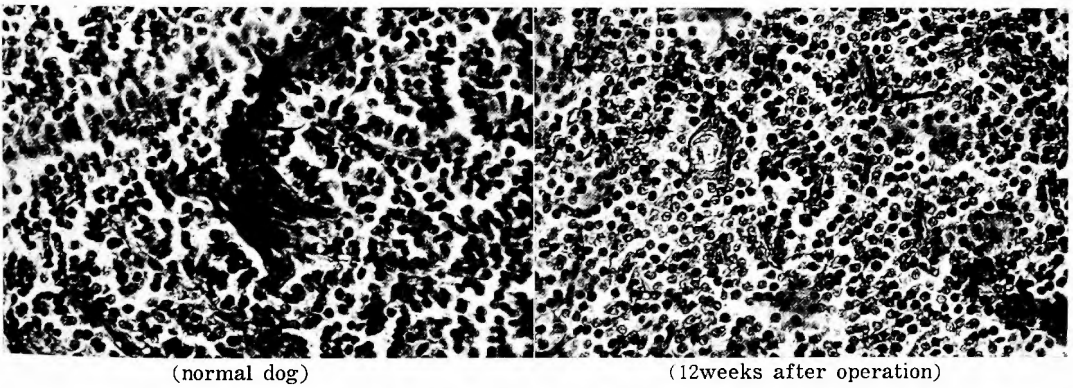
(5~12 weeks after operation)

Photo. 9 Parathyroid gland Photo. 10



(normal dog) (10weeks after operation)

Photo. 11 Photo. 12



(normal dog) (12weeks after operation)

alkalin phosphatase, while hypofunction results in its decrease. I determined the alkaline phosphatase level by BODANSKY's method with the electrophotometer in order to find alteration of the parathyroid gland activity after total pancreatectomy.

(B) RESULTS

Morphologically, as compared with the control animals, neither enlargement and hyperplasia nor atrophy and hypoplasia was observable, nor could I find any water-clear cells which might suggest hyperfunction nor proliferation of connective tissue which might suggest sclerosis, as shown in the photograph 1, 2, 10, 12. The same findings were also obtained in the human case as shown in the photograph 3, 4.

In the experiments on oxalate tolerance, I could obtain no significant result, as shown in Fig. 3.

The results of the determination of serum alkaline phosphatase is shown in Fig. 4. The curves showed some increments which suggested hyperfunction of the

Figure 4

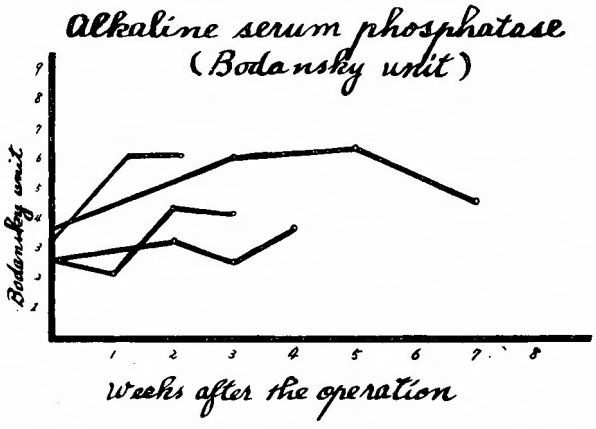
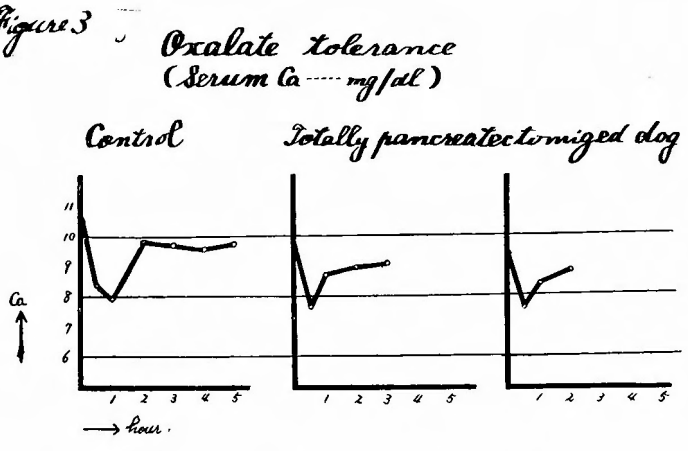


Figure 3



parathyroid glands, but these increments were within the normal range.

From all of these data I am obliged to presume that in animal experiments

the parathyroids take an active part within almost the normal range through the whole postoperative course. Accordingly in my experiments, although the fact that tetany condition accompanied by a decrease in the serum diffusible calcium which I found in one clinical case suggested strongly the existence of hypofunction of the parathyroid, I could find no changes in their attitudes.

DISCUSSION

As a result of my research for changes in calcium metabolism after total pancreatectomy, I found that in all cases there existed a negative calcium balance.

According to Mc Gowan, hydrochloric acid is one of the most important agencies for the absorption of the alkaline earth elements and especially of calcium phosphate. With normal gastric acidity, compounds of calcium with weak organic acids are converted into the chloride, which is absorbed easily from the stomach and the duodenum.

If gastro-duodenectomy is performed simultaneously with total pancreatectomy, absorption may be disturbed because of the lowering of the gastric acid.

While solution of calcium salts by the gastric juice is important, it is by no means an indispensable factor. According to Curry, Schmidt, and Greenberg, the absorption will, in large part, depend on the time during which the food remains in the intestines.

Using a diet mixed with carbon powder, I found that the time during which the food remains in the intestines is shortened after total pancreatectomy. This suggests that there is not an ample time for the calcium as well as other nutriments to be absorbed in the intestines and it may be one of the reasons for the digestive disturbances after total pancreatectomy.

Moreover, Boyd, Crum, Lyman have pointed out that adequate amounts of fatty acids aid the digestion of calcium, but that if fatty acids are excessive, calcium is excreted as insoluble calcium soap resulting in the lowering of calcium absorption.

Accordingly, it may well be assumed that the digestive disturbance of fat is one of the causes of decreased absorption of calcium after total pancreatectomy. At the same time the digestive disturbance of fat interferes with the absorption of the fat soluble vitamins, especially vitamin D and leads to a deficiency of that vitamin.

Animals which have been maintained for certain periods of time on a diet deficient in vitamin D are said to be in negative calcium balance. Furthermore, vitamin D deficiency hinders the deposition of calcium in bone, and this together with the negative calcium balance leads to the consumption of one-third to one-half of the calcium in the bone three to twelve weeks after the operation, and sometimes even osteoporosis is produced.

The serum calcium level showed sometimes some decrease and some flucutuation, but in all cases I found a decrease in the serum protein levels, and there were no changes in the diffusible calcium which is probably physiologically active.

This fact indicates that the hypocalcemia after the operation is due to a decrease in the non-diffusible calcium, caused by hypoproteinemia followed by negative N balance. Consequently the determination of serum protein must not be omitted in conjunction with that of serum calcium. I have received many reports which stated that in cases of decreased calcium absorption such as sprue, celiac disease etc. the patients develop hypocalcemia. But in most cases disturbance of protein absorption existed at the same time so that hypoproteinemia would be present, accordingly the serum non-diffusible calcium would be decreased and there would be almost no change in the serum diffusible calcium.

The parathyroid hormone apparently regulates the level of diffusible calcium. So far as the parathyroid glands take an active part in the normal range, the diffusible calcium is always within the normal range in spite of a decrease or increase in calcium absorption.

I could find no significant abnormality of the parathyroid glands after the operation either histologically or biochemically.

Doyle, Nonidez, Goodale, Sheard, et al. reported that a domestic fowl which had been maintained for some time on a vitamin D deficient diet developed bone decalcification and hyperplasia of the parathyroid glands. Oberling, Guerin, Pal et al. confirmed this finding in mammals. Tammann in 1928, Loeweg in 1931, Jung et al. found enlargement and hyperplasia of the parathyroid glands in the presence of vitamin D deficiency caused by interference with calcium absorption from the gastrointestinal tract by means of a biliary fistula.

These studies, both experimental and clinical, indicated that in the presence of vitamin D deficiency and interference with calcium absorption, enlargement and hyperplasia of the parathyroid glands occur secondarily and hyperparathyroidism results.

However, I could not find enlargement and hyperplasia of the parathyroid glands in any of our cases in spite of the presence of low calcium absorption accompanying vitamin D deficiency after total pancreatectomy.

But one patient of our series revealed, as stated before, symptoms of tetany eight months after the operation, and, at the same time, showed a decrease in serum diffusible calcium, and this patient recovered soon after an adequate intake of calcium. This case undoubtedly suggested that the temporary hypofunction of the parathyroid glands occured although there was no histological abnormality.

These facts seem to indicate that the changes in calcium metabolism after the operation are due not only to the abolishment of the external secretion of the pancreas but also to the disappearans of its endocrine function which may influence the parathyroid glands secondarily by some means.

CONCLUSION

In order to study the changes in calcium metabolism after total pancreatectomy, I have made some studies on totally depancreatized dogs and men.

The results may be stated as follows ;

(1). Dogs as well as human patients tend to develop a negative calcium balance after total pancreatectomy.

(2). I found a mild fluctuation and decrease in the serum calcium level. This is due to a decrease in the non-diffusible calcium fraction because of hypoproteinemia. Nevertheless the diffusible calcium fraction, which porbably is physiologically active, was found to be within a normal range in all cases for nine to twelve weeks after the operation, except for one clinical case.

(3). In animals one third to one half of the bone calcium is exhausted three to twelve weeks after the operation, and osteoporosis is often found on histological examination.

(4). When vitamin D deficiency with decreased calcium absorption takes place, it may be reasonable to find enlargement and hyperplasia of the parathyroid glands. However, I could find no enlargement or hyperplasia of the parathyroid glands, and there were no laboratory data to suggest hyperfunction of the parathyroid glands during the whole course after total pancreatectomy, in spite of the fact that vitamin D deficiency and disturbances in calcium absorption were present.

One patient in our series revealed symptoms of tetany and showed the lowering of the serum diffusible calcium eight months after total pancreatectomy. Therefore, it is advisable not to neglect the possibility of calcium deficiency in man after the operation, although the true mechanism of inducing calcium deficiency has not yet been established.

I wish to thank Prof. Dr. Chisato Araki and Assist. Prof. Dr. Ichio Honjo for their guidance throughout the period of this work.

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和文抄録

膵全切除後のCa代謝に就いて

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膵全切除後数ヵ月を経過した1患者がテタニー様症状を起し，この症状はCaの静注により軽快する事実に遭遇した．この事実は膵全切除後Ca代謝に変化が起る事を示しているものと思われる．そこで膵全切除後のCa代謝を動物実験及び臨床例に就いて2,3の方面より追及し，得た新知見を報告する．

1) 人でも犬でも膵全切除後はCaの出納は負の値を示す．是は術後腸内容の通過速度が著しく早くなりCaが吸収されるに充分な腸内停滞時間がなく，更に脂質の吸収障害がある為多量の脂肪及び脂肪酸がCaと共に排出されると同時に脂溶性ビタミン，殊にビタミンDの欠乏が加わりCaの腸内排出がたかまつた為である．

2) 血清Ca濃度は軽度の変動及び低下を認めるが何れも術後蛋白質の吸収低下の為，低蛋白血症を来し蛋白と結合せる非透析性Ca濃度の低下を来した為であり，生理的役割を演ずる透析性Ca濃度は1臨床例に軽度の低下を認めた以外全例に於て変動低下はなかつた．

3) ビタミンDの欠乏は骨へのCa沈着を妨げ，Caの吸収低下と相俟つて骨のCaの消耗を惹起し，3～12週の間に1/3～1/2の脱灰を来し，Osteoporoseの像を示す様になる．

4) Caの吸収低下とビタミンD欠乏のある場合上皮小体の肥大と増殖を来し二次的機能亢進を認めるものであるが膵全切除後はCaの吸収低下とビタミンD欠乏があるに拘らず全例に於て上皮小体の肥大及び増殖を認めず，又機能亢進を推測せしめる事実もなく，加えて1臨床例にテタニー様発作を認めた事はその機能低下を推定せしめるものであり，この様な合併症が膵全切除後に起り得ると云う可能性を示すものと考える．