原　　著

THYROID AND PANCREAS: THYROID FUNCTION OF THE COMPLETELY DEPANCREATIZED DOG TREATED WITH INSULIN

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I. INTRODUCTION

In recent years, extensive pancreatectomy against pancreatic cancer has become more popular operative procedure in the field of surgery. Not a few cases require a complete pancreatectomy. Diabetes mellitus which is naturally caused by the complete pancreatectomy can be well controlled without showing the development of life-threatening defeciency symptom by continuous administration of insulin at suitable dose. As to the function of the endocrine system in diabetics, an unanimous theory has not yet been established. Concerning the thyroid function also, one of the endocrine system, in diabetics, there have been much discussed.

It has already been reported by many investigators that temporary hyperglycemia or glycosuria is frequently observed in hyperthyroidism. As early as in 1909, LICINI noticed histologically hyperthyroidism following the total pancreatectomy. HOUSSAY observed degeneration in residual Langerhans' islets and development of diabetes mellitus in partially depancreatized dogs when fed by thyroid diet, and named it metathyroid diabetes. In recent years, there is a report of hyperthyroidism due to total pancreatectomy by YOSHIOKA.

Taking into consideration the complexities of diabetes due to total pancreatectomy, it is difficult to assume that the thyroid remains for long in a state of hyper- or hypofunction. Namely, diabetes due to total pancreatectomy is characterized by following features; (1) far smaller dose of required insulin compared to that required in severer cases of internal diabetes commonly seen, (2) progressive loss of body weight, (3) deve-

lopment of fatty liver. YAMAMOTO and OSHITANI have made it clear that the continuous administration of insulin at suitable dose lessens the degree of progressive loss of body weight and prevents the development of fatty liver in early postoperative stage as well as later. In the present experiments, it was revealed that there exsist some differences between thyroid function of dogs whose diabetes due to total pancreatectomy is well controlled with insulin of suitable dose and that treated with insulin of insufficient dose.

The present experiment was designed to study the change in thyroid function of completely depancreatized dogs concerning following items; thyroid uptake of radio-active iodine (abbreviated to Thyroid ^{131}I uptake), blood-plasma protein-bound radioactive iodine conversion ratio (abbreviated to PB ^{131}I C. R.), serum protein-bound iodine (abbreviated to PBI), TSH-test, weights of the thyroid gland, histological findings and somnolent metabolism. At the same time, interaction between thyroid and pituitary gland was also studied.

II. MATERIALS AND METHODS

1) Materials

Adult mongrel dogs weighing 6 to 16 kg were employed, which were fed by well boiled diet consisted of rice, wheat and fish, both pre- and postoperatively.

2) Methods

i) Anesthesia

Under the basal anesthesia with intramuscular injection of Cocktelin-H (5mg/kg), Isozol was injected intravenously at a dose of 0 02 to 0 048g per kg body weight.

ii) Sterilization

Operation field was sterilized with Mercurochromealcohol solution of 2 %.

iii) Operative procedure

Laparotomy was performed by the upper median incision. The duodenum wass exposed. Reaching the duodenal lobe of the pancreas, which is adjoining to the duodenum, the branches of the pancreatoduodenal vessels were doubly ligated and divided and the pancreas was isolated. Then the branches from the splenic vessels, which are distributed to the free lobe of the pancreas, were ligated and cut. Here the pancreas was completely removed. Before closing the abdomen, 50 to 100ml of chondroitic acid of 1 % was poured into the peritoneal cavity, in order to prevent the postoperative adhesion.

iv) Postoperative management

The dogs were fed twice a day with well boiled diet of rice, wheat and fish postoperatively. Insulin was injected subcutaneously at a dose of 1 to 3 u./kg, which was administered twice a day after meal. Insulin used was a product of Shimizu Seiyaku Co. 'Isujilin Shimizu'.

v) Blood samples

Blood samples were taken chiefly from the femoral vein in the early morning in a fasting state, before the operation and every week from the first to twelveth week postoperatively. In some cases, blood was taken for longer period. The blood sample were immediately used for the examinations.

vi) Thyroid ^{131}I uptake

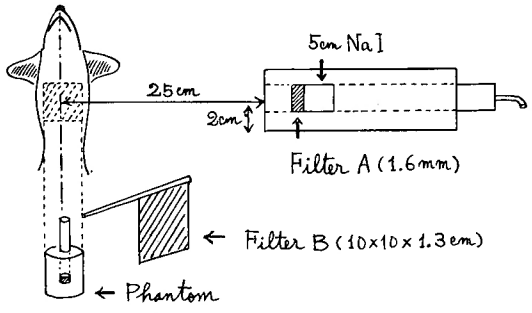
Radioactive iodine (^{131}I) was injected into the femoral vein at a dose of 50 to 100 μ°C. Radioactivity of the thyroid region was measured at 24 hours after the injection by scintillation counter (Kobekogyo Co). The procedure of the measurement is shown in Fig. 1. In order to exclude the portion of longer wave of gamma rays that misleads the data, the region was shielded by lead, filter A. The counts of background of the body was measured by shielding the thyroid region with filter B. Radioactivity of ^{131}I of the same dose as administered was measured placing it in a phantom made by Kaken. Thyroid ^{131}I uptake was calculated from following formula.

$$\text{Thyroid } ^{131}I \text{ uptake} = \frac{\text{Dog (A) cpm} - \text{Dog (AB) cpm}}{\text{Phant. (A) cpm} - \text{Phant. (AB) cpm}}$$

vii) PB^{131}I C. R.

Radioactive iodine, having activity of 50 to 100μ°C, was injected into the femoral vein. From the femoral vein of the other side, about 3 ml of blood was taken, which was put into a test tube containing salts of oxalic acid. After mixing the content together, the plasma was separated by centrifugation, 1 ml of which was put into test tube of thick wall and its radioactivity was measured in the well-type scintillation counter. Then, 5cc of 10% acetic acid trichloride was added to the plasma to precipitate protein and the content was centrifugated again. The supernatant was discarded, acetic acid trichloride was added to the precipitate again, and stirred by a glass stick, centrifugated and the precipitate was washed twice. Radioactivity of the precipitate was measured immediately again.

Fig. 1 Method of Thyroid ^{131}I Uptake.



$$\text{Thyroid } ^{131}I \text{ Uptake} = \frac{\text{dog (A) e.p.m.} - \text{dog (A.B.) e.p.m.}}{\text{Phaatom (A) e.p.m.} - \text{Phantom (A.B.) e.p.m.}}$$

$$\text{PB } ^{131}I \text{ C. R.} = \frac{\text{Radioactivity of PB } ^{131}I}{\text{Radioactivity of total blood-plasma } ^{131}I}$$

viii) PBI

The concentration of serum PBI was assayed by the method of BARKER-HEKI. The procedure is summarized as follows.

Reagents :

All the reagents used were prepared using redistilled water, which had been distilled from once distilled water to which caustic potash was added as 1 to 2%, added in a glass equipment. Reagents of utmost purity were used. Iodine slightly contained in the reagents was eliminated, when necessary.

a. Reagents for deproteinization
   1. 10% zinc sulfate solution
   2, 1/2N caustic soda solution
b. 4N sodium carbonate solution

Sodium carbonate exsiccated of special purity was used for this purpose.

c. 2N hydrochloric acid

d. 7N sulfuric acid

Three to 5cc. of hydrochloric acid was added to 500 cc of concentrated sulfuric acid, which was boiled for 60 minutes. Iodine that may probably be contained was eliminated by gradual cooling.

e. 0.1N sodium arsenite solution

Twenty-five cc of 4% caustic soda was added to 4.95 g of well dried exsiccated arsenious acid and completely solved by heating in water bath. After cooling down 300 cc of water was added and about 4 cc of 7N sulfuric acid added until the reaction showed slight acidity. Water was again added as to make the solution 1000 cc in all.

f. 0.02N ceric acid solution

Ceric acid Ce $(SO_4)_2 \cdot 4H_2O$ (Merk) of 9.3 g was solved in 500 cc of water. A clear light yellow liquid was obtained by adding 230 cc of 7N sulphuric acid. This was diluted with water to 1000 cc in all. The concentration of cerium solution was accurately adjusted to 0.02N by titration with 0.02N oxalic acid at a temperature of 80°C in water bath.

g. 0.0002M ferroin solution

Ferroin (O-phenanthroline-ferrous complex) solution of 0.025M was diluted 125 times with water at use.

Procedure of PBI level determination.

On the first day, 8 cc of water, 1 cc of 10% zinc sulfate and 0.5 cc of N/2 caustic soda were added in the mentioned order to 1 cc of serum separated from blood sample. These were mixed together adequately and centrifuged for 10 minutes at a frequency of 2000 r. p. m. The supernatant was discarded and the precipitate was washed twice with 25 cc of water for each time. Furthermore, 1cc of 4N sodium carbonate solution was added to twice washed precipitate and mixed together. This was dried in the drier heated to 80 to 90°C.

On the second day, the material was heated and calcinated in the electric furnace for an hour and a half at 600±25°C.

On the third day, after gradual cooling down, 2 cc of 2N hydrochloric acid and 2 cc of 7N sulfuric acid were added to the material, which was diluted by water to 7 cc in all after small bubbles had disappeared that had been seen when hydrochloric acid and sulfuric acid had been added. The material was well mixed and centrifuged for 10 minutes at 2000 r. p. m. Clear supernatant of 3.5 cc was pipetted into a test tube for tintometry.

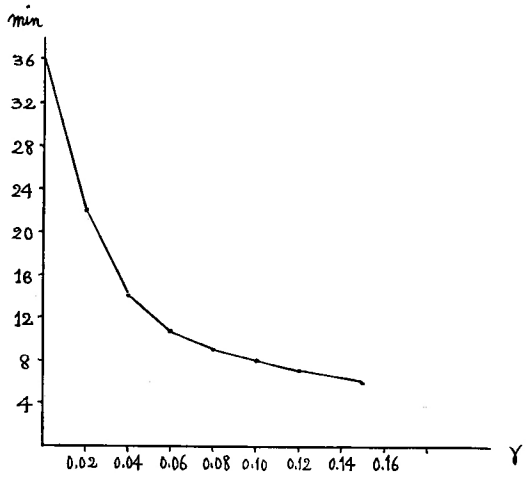
To the material, 1 cc of sodium arsenite solution was added and put into water bath of 60°C until the temperature was balanced. Then, 2 cc of cerium solution which had been previously heated to 60°C was added to the content of the tube, and at the same time the timer was let work. The tincture of cerium solution gradually fades according to the amount of iodine contained in the material. As the tincture almost faded, 0.3 cc of the material was pipetted into another small tube which contains 0.1 cc. of ferroin solution. Here the seconds were counted in which the content of the small tube is tinctured red. Thus the amount of iodine contained in 1 cc of the serum is known from

the standard curve later mentioned. Since only one half of the material was used for determination in this procedure, the value obtained from the standard curve should be duplicated.

Standard curve.

Two cc of 2N hudrochloric acid, 2 cc of 7N sulfuric acid and 2 cc of standard solution of iodine (KI: Merk was used. The solution was adjusted to contain 0.02 to 0.15 gamma of iodine per 1 cc) were added to 1 cc of 4N sodium carbonate solution. After centrifugation for 10 minutes at a frequency of 2000 r. p. m., 3.5 cc of the supernatant was taken and the time was recorded in the same procedure as mentioned above. The standard curve was drawn taking seconds in y-axis and concentration of iodine in x-axis (Fig.2)

Fig. 2 P.B.I.: Standard curve (60°C)



Remark

By heating sodium carbonate to a high temperature as 600°C, time required for the fading of tincture of cerium solution is apt to be slightly shortened. Therefore, at every determination, the time for fading of sodium carbonate alone should be estimated as blank and this must be taken into consideration of the value actually observed.

ix) TSH-test

The test was made following the method of JEFFERIES.

Method

Radioactive iodine of 10μC was injected into the femoral vein in fasting state and 3 hours later thyroid ^{131}I uptake was measured. At the same time blood sample was taken and serum protein-bound iodine level was determined (3-hour thyroidal ^{131}I uptake and PBI). Immediately after this determination, TSH was injected intramuscularly at a dose of 100 Ms u. On the next day, i. e. 21 hours after the injection of TSH, residual radioactivity of the thyroid region was measured. Radioactive iodine of 10 μC was again injected into the femoral vein and 3 hours later thyroidal ^{131}I uptake and serum PBI level after the administration of TSH was determined. At measuring post-TSH thyroidal ^{131}I uptake, the radioactivity of the thyroid region measured previously to the 2nd injection of radio-active iodine was taken into account and physical diminish of radioactivity was corrected. Pretiron (Schering) was used as TSH. Procedure of TSH-test is briefly summarized in Fig. 3.

x) Weights of the thyroid gland

The animal was slaughtered by intravenous injection of 3 % potassium chloride of 20cc. The thyroid gland was taken out immediately after the death and weighed in the balance.

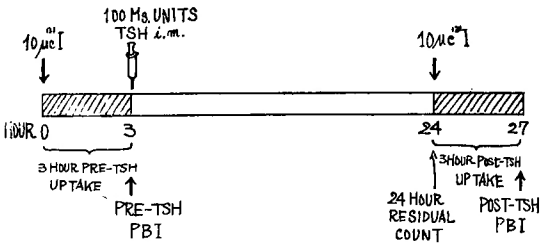
xi) Histological findings of the thyroid gland

The gland was immediately fixed in 10% formalin solution and stained with hematoxylin and eosin.

xii) Somnolent metabolism

Isozol (0.03 to 0.048/kg) was injected into the femoral vein of the dog that had been starved at least for 12 hours. As the dog fell asleep endotracheal tube with cuff was inserted. The cuff was swollen and the tube was aonnected to Knipping's apparatus (Ichikawa-Shiseido Co.). After the respiration and pulse had become quiet and gentle, somnolent metabolism was estimated. Respiratory coefficient was calculated from oxygen volume consumed and carbon dioxide volume expirated.

Fig. 3 Technic of TSH test.



III. RESULTS

1. Thyroid ^{131}I uptake

i. Before the operation

Twenty-four-hour thyroid ^{131}I uptake in adult dogs was measured to be 10.8 % on the average, which coincides approximately with the value reported by FREDRICKSON. (Tab. 1)

ii. Postoperative fluctuation

As shown in Tab. 1, the average value of 24-hour thyroid ^{131}I uptake shows a tendency of gradual decrease after the operation, that is, at the 4th postoperative week it ranged 9.0 %, at the 8th week 6.2 % and at the 12th week 5.8 % each on the average.

Tab. 1 Pre-, and postoperative thyroid ^{131}I uptake (%)

Dog No.	Insl. u/kg	Before operat.	Weeks after Operation 4	8	12
2	1	4.6	5.0		
10	1	7.7	3.8		
12	1	3.4	4.1		
13	2	15.4	12.0		
14	3	13.1	15.0	4.9	5.3
15	3	3.0	8.5	8.7	5.9
17	2	21.0	5.7	2.7	1.4
18	2	20.0	21.4	5.1	7.7
22	2	12.0	6.3	9.7	
24	1	7.1	8.1		
Mean		10.8	9.0	6.2	5.8

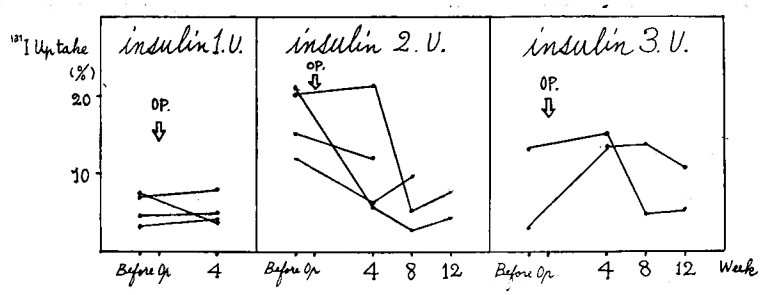
As to the corelation between insulin doses administered and thyroid ^{131}I uptake, in the group of dogs administered with 1 to 2U/kg of insulin, thyroid ^{131}I uptake showed little change at the 4th week, it showed decreased level at the 8th week and slightly increassed level at the 12th week.

On the other hand, in the group which received 3U/kg of insulin, it increased slightly at 4th postoperative week, then decreased at the 8th week and it decreased on further, at the 12th week. Less cases survived for long in the former group compared to the latter. Accordingly, it can be at least, pointed out that postoperative fluctuation in thyroid ^{131}I uptake varies according to the dose of insulin administered. (Fig. 4)

2. PB ^{131}I C. R.

PB ^{131}I C. R. ranged before the operation 6.8% on the average, which decreased to

Fig. 4 Thyroid ^{131}I Uptake and various insulin doses



3.0% 4 weeks after the operation, maintaining as low a level as 4.6 % until the 8th week and it increased up to 6.1 % on the average 12 weeks after the operation showing a tendency to get back to the level before the operation. (Tab. 2)

As to the corelation between PB ^{131}I C. R. and insulin sodes, the similar tendency was observed in all groups, that is, decrease at the 4th week, slight increase at the 8th week and approximate restoration to preoperative level toward the 12th week. (Fig. 5)

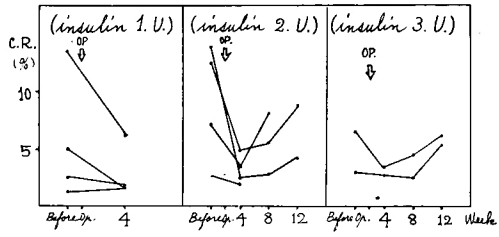
Tab. 2 Pre-, and postoperative PB^{131} I C.R. (%)

Dog No.	Insl. u/kg	Before operat.	Weeks after Operation 4	8	12
2	1	13.6	6.4		
10	1	2.6	1.9		
12	1	5.0	1.7		
13	2	2.6	2.0		
14	3	3.0	2.7	2.5	5.3
15	3	6.5	3.4	4.5	6.1
17	2	12.5	4.8	5.5	8.7
18	2	13.9	2.5	2.8	4.2
22	2	7.1	3.5	7.9	
24	1	1.3	1.5		
Mean		5.8	3.0	4.6	5.1

3. PBI level

PBI level ranged before the operation 5.8γ/dl on the average, which increased to 6.7γ/dl in the lst week, then decreased gradually as time went on, that is, 5.4γ/dl at the 4th week, 4.7γ/dl at the 8th week and 4.2γ/dl at the 12th week. (Tab. 3)

Fig. 5 P.B. ^{131}I.C.R. and various insulindoses



As to the corelation between insulin doses and PBI level, PBI level increased in the first week which was followed by a gradual decrease with weeks, showing a similar tendency in all groups. (Fig. 1,2,3,6)

4. TSH-test

The test was carried out after the method of JEFFERIES. Thyroid ^{131}I uptake and serum PBI level were taken as the indication of the thyroid function.

i. TSH-test taking thyroid ^{131}I upatke as an indicator Thyroid ^{131}I uptake increased by the administration of TSH.[15]

In normal dogs, thyroid ^{131}I uptake ranged from 3.5 % to 40.8 % with a mean of

Tab. 3 Pre-, and postoperative PBI level (γ/al)

Dog No.	Ins. u/kg	Preop.	Weeks after Operation 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
2	1	6.5	7.8	6.5	5.9	5.4	+											
10	1	6.2	7.2	6.0	5.5	5.0	+											
12	1	5.9	6.8	6.1	5.4	5.9	+											
13	2	5.0	5.6	4.5	5.3	5.4	+											
14	3	5.3	5.6	4.9	5.2	4.9	5.0	4.8	4.8	4.5	5.2	5.2	4.4		5.3	4.0	4.0	5.0
15	3	5.4	6.0	5.2	5.2	5.5	5.2	5.0	5.0		5.2	4.4	4.1	4.0		5.0	4.5	4.6
17	2	5.5	6.6	6.0	4.9	5.5	5.3	5.2	5.0	4.8	4.4	4.5	4.4	4.0	4.3	+		
18	2	6.4	7.4	5.5	5.9	5.9	5.0	5.0	5.0	4.8	4.4	4.5	4.5	4.5	4.2	+		
22	2	5.9	6.8	5.0	4.4	5.0	5.2	5.2	4.9	4.5	4.6	+						
24	1	5.5	6.3	4.4	4.4	+												
Mean		5.8	6.7	5.4	5.2	5.4	5.2	5.1	4.9	4.7	4.8	4.7	4.4	4.2				

Fig. 6 P.B.I. and various insulin doses.
(1) Insulin 1. U.

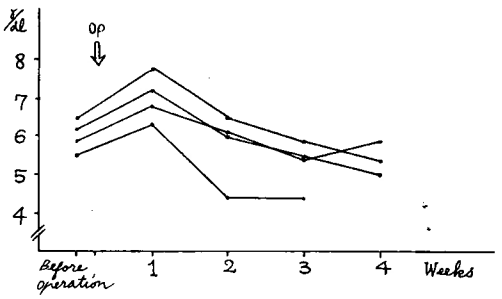


Fig. 6 (2) Insulin 2. U.

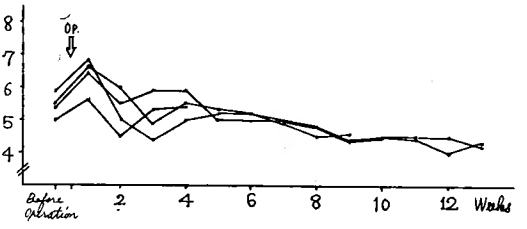
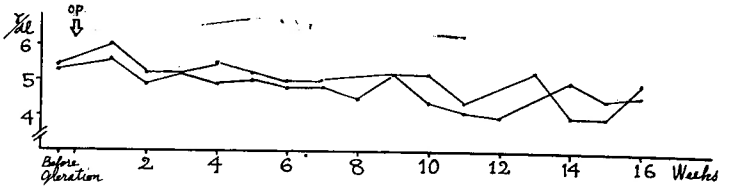


Fig. 6 (3) Insulin 3. U.



10.4 %, which increased by the administration of TSH (100 Ms u.) to 7.5% to 65.3% with a mean of 22.1 %. The rate of increase was 133.9 % on the average. At the 4th postoperative week, pre-TSH thyroid ^{131}I uptake ranged 6.3 % to 21.4 %, and it increased after the administration to 9.0 % to 22.2 %. The rate of increase was 27.0 % on the average. Among these three cases of negative rate were observed. At the 8th week, pre-TSH thyroid ^{131}I uptake ranged from 2.7 % to 8.7 %, which increased after the administration to 6.9 to 16.3 %. The rate of increase was 98.4 % on the average. In short, it is assumed from TSH-test taking thyroid ^{131}I uptake as an indication that thyroid reserve diminishes remarkably 4 weeks after the surgery, which shows tendency to appr-

Tab. 4 TSH-test taking thyroid ^{131}I uptake as its indication (%)

Dog No.	Insl. u/kg	Before Oper.			After Operation								
					4th. Week			8th. Week			12th. Week		
		a*	b**	r. i.***	a	b	r. i.	a	b	r. i.	a	b	r. i.
2	1	5.5	17.8	223.8	7.2	9.0	27.8						
10	1	40.8	65.3	60.0	18.7	16.1	13.9						
12	1	15.9	41.3	159.3	9.6	9.2	4.2						
24	1	7.1	14.6	105.6	8.1	11.5	42.0						
13	2	5.4	14.0	159.2	12.0	15.4	28.4						
17	2	7.9	18.9	139.2	5.7	10.6	86.2	2.7	7.7	185.2			
18	2	7.5	17.6	148.0	21.4	22.2	3.7	5.1	9.2	80.4			
22	2	3.5	7.5	114.0	6.3	9.6	52.3						
14	3	3.6	8.3	130.5	15.0	13.1	12.7	4.9	6.9	40.8	3.7	7.1	91.9
15	3	6.5	15.5	139.0	8.5	13.6	60.0	8.7	16.3	87.3	5.9	11.9	101.8
Mean		10.4	22.1	133.9	11.2	14.0	27.0	5.4	10.0	98.4	4.8	9.5	96.8

Rate of Increase $= \frac{b-a}{a} \times 100$ (%) a: Pre-TSH value b: Post-TSH value

a*: Pre-TSH value b**: Post-TSH value r. i.***: Rate of increase

oach from lowered level to preoperative one after the 8th week. (Tab. 4)

As to the corelation between insulin doses and the fluctuation of thyroid ^{131}I uptake at TSH-test, the rate of increase of thyroid ^{131}I uptake diminished all 4 weeks after the operation, which showed increase at the 8th week, showing a similar tendency in all groups. This reveals the fact that the thyroid maintains the function to respond to TSH and ability to recover its reserve which once diminished shortly after the operation.

ii. TSH-test taking serum PBI as an indicator.

PBI level increases by the administration of TSH. In normal dogs PBI level ranged from 5.0 to 6.2 γ/dl, with a mean of 5 6 γ/dl, which increased to 5.9 to 7.6 γ/dl, with a mean of 6.9 γ/dl after the administration of TSH (100 Ms u.). The rate of increase was 21.4 % on the average. At the 4th postoperative week, pre-TSH PBI level ranged

Fig. 7 Thyroid ^{131}I Uptake and various insulin doses.

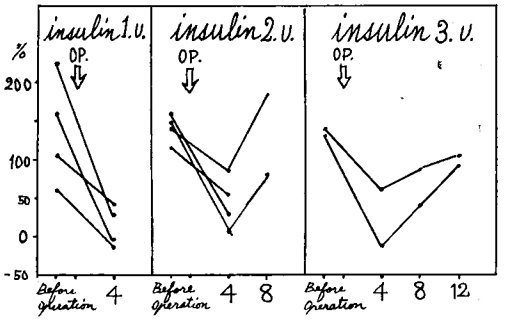
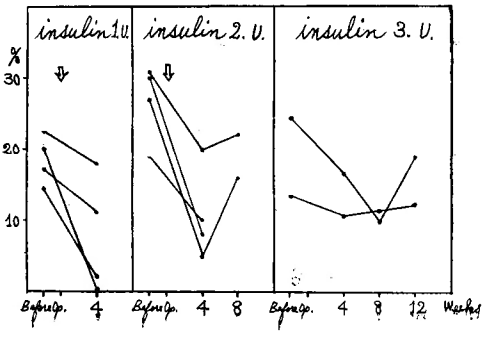


Fig. 8 Rate of increase in P.B.I. and various insulin dosis.



Tab. 5 TSH-test taking PBI level as its indication (%)

Dog No.	Ins. u/kg	Before Ope. a*	b**	r. i.***	After Operation 4th. Week a	b	r. i.	8th. Week a	b	r. i.	12th. Week a	b	r. i.
2	1	6.2	7.5	17.3	5.1	5.7	11.7						
10	1	6.2	7.6	22.6	5.5	6.5	18.2						
12	1	5.9	7.4	20.3	5.9	5.9	0						
14	1	5.5	6.3	14.5	4.4	4.5	2.3						
13	2	5.0	6.5	30.0	5.5	6.0	8.3						
17	2	5.5	7.2	30.9	5.0	6.0	20.0	4.5	5.5	22.2			
18	2	5.5	7.0	27.2	5.9	6.2	5.1	4.9	5.7	16.3			
22	2	5.9	7.0	19.0	5.0	5.5	10.0						
14	3	5.3	6.6	24.6	4.9	5.7	16.3	5.0	5.5	10.0	5.8	6.9	18.9
15	3	5.2	5.9	13.5	5.5	6.1	10.9	5.4	6.0	11.2	4.0	4.5	12.5
Mean		5.6	6.9	21.4	5.3	5.8	11.5	5.0	5.7	15.2	4.9	5.7	15.2

Rate of increase $= \frac{b-a}{a} \times 100$ (%) a: Pre-TSH value b: Post-TSH value

a*: Pre-TSH value b**: Post-TSH value r. i.***: Rate of increase

from 4.4 to 5.9 γ/dl, with a mean of 5 3 γ/dl, which increased after the admnistration to 4 5 to 6 5 γ/dl, with a mean of 5 8 γ/dl. The rate of increase was 11 5% on the average. At the 8th week, pre-TSH PBI level was 5 0 γ/dl on the average, which increased to 5.7 γ/dl on the average after the administration of TSH. The rate of increase was 15 2 % on the average. That is to say, in the fluctuation of serum PBI level at TSH-test, the rate of increase diminished, 4 weeks after the operation, to as low a level as a half of the preoperative level, which showed a slight rise 8 weeks after the operation (Tab. 5). As to the corelation between insulin dcses and the rate of increase in PBI, the rate decreased 4 weeks after the operation being followed by a slight increase at the 8th week, showing the similar tendency in all groups. (Fig. 8).

From this result, it can be assumes, similarly to the above mentioned thyroid ^{131}I uptake, that thyroid reserve restores gradually, which once has diminished after the surgery, and the thyroid maintains the function to respond to the administration of TSH.

5. Weights of the thyroid gland

The thyroid glands were taken out and weighed immediately after animals' death or slaughter with intravenous injection of 20 cc. of 3% potassium chloride. Thyroid glands in normal dogs weighed from 1.75 to 1 00 g, with a mean of 1 24 g, while in the completely depancreatized dogs, the weight decreased after the surgery, accompanied with body weight loss. The gland weighed 0 53 to 1.10 g, with a mean of 0.78 g within the first week, 0.48 to 0 88 g with a mean of 0.66 g at the 2nd week, 0.35 to 0.75 g, with amean of 0.60 g at the 4th week, 0.70 g to 0 80 g, with a mean of 0.75 at the 5th week, and 0.50 to 0.70 g, with a mean of 0.66 g at the 13th week. Furthermore, the proportion of the weight of the thyroid gland to body weight was 0 0132 % in normal dogs, while in the dogs operated on it being 0.0118 % at the lst week, 0.0104 %

at the 2nd week, 0.0105 % at the 4th week, 0.0106 % at the 5th week and 0.0104 % at the 13th week, showing an apparent decrease. (Tab. 6, 7)

6. Histological findings

In normal dogs, small follicles and large ones are scattered about at random. The follicle has one layer of epithelial cells, the cells being cubic in their shape and bearing oval or almost circular nuclei situated in the midst of the cytoplasma. (Plate 1. 2.)

One week after total pancreatectomy, the size of the follicles was observed to be remarkably diversified, each follicle being detached from the adjoining ones. There was also observed a proliferation of the connective tissue in the stroma. The histological appearance was featured by diminish of the large follicles and increase in the small ones. In small follicles colloid was not observed. These changes were widely observed in the parenchym of thyroid gland. Where the small follicles are conglomelated, epithelial cells were larger and a little brighter, bearing larger nuclei containing less chromatin compared to those of normal follicle. Nuclear corpuscles were readily observed. (Plate 3. 4.)

Two weeks after the operation, most of the follicles were seemed to have changed small, their epithelial cells being cubic and slightly flattened. Fibrosis of a slight degree could be observed in the stroma. Colloidal content of the follicle included basophilic substance of irregular shape, which was stained partly dark, partly bright. (Plate 5. 6.)

Four weeks after the operation, small follicles increased more conspicuously, accompanied with an increase in the connective tissue in the stroma. In some areas degeneration was observed, containing colloid stained partly dark,

Tab. 6 Body weight and weight of thyroid gland in normal dogs

Dog No.	Weight of thyroid g	Body weight kg	Proportion to body weight (%)
1	1.00	10	0.0100
2	1.20	8	0.0150
3	1.18	7	0.0149
4	1.75	14	0.0125
5	1.34	8	0.0168
6	1.10	7	0.0157
7	1.08	10	0.0108
8	1.12	10	0.0112
9	1.07	8	0.0125
10	1.54	12	0.0126
Mean	1.24	10	0.0132

Tab. 7 Body weight and weight of thyroid gland in completely depancreatized dogs

Dog No.	Weight of thyroid g	Body weight kg	Proportion to body weight (%)	Date of death
8	0.53	6	0.0038	7
9	1.10	8	0.0138	8
21	0.70	6	0.0116	7
23	0.80	6	0.0133	7
11	0.70	7.5	0.0093	13
7	0.75	9	0.0083	15
6	0.55	3.5	0.0157	16
25	0.80	7.5	0.0107	16
26	0.35	5	0.0070	23
2	0.75	5	0.0150	28
30	0.70	6	0.0117	29
24	0.60	7	0.0086	29
10	0.72	5	0.0144	33
13	0.80	10	0.0030	33
12	0.75	8	0.0094	34
22	0.65	7.5	0.0087	63
32	0.80	9	0.0099	80
17	0.50	5.5	0.0091	91
18	0.70	5.5	0.0116	91
34	0.88	7	0.0125	125
14	0.50	9	0.0056	224

partly bright. (Plate 7. 8.)

Ten weeks after the operation, findings were roughly similar to those observed 4 weeks after the operation, being scattered with Hurthle-like cells here and there. (Plate 9. 10)

Eithteen weeks after the operation large follicles disappeared and were replaced by small follicles and prosperous proliferation of epithelial cells without colloidal content, the masses of epithelial cells being consisted of epithelial cells alone. This conspicuous proliferation of follicular epithelial cells obviously differs from the papillary proliferation protruding to the inner space of the follicles which is commonly observed in cases of so-called hyperthyroidism. (Plate 11. 12)

To summarize these findings, the changes in thyroid gland of completely depancreatized dog are (1) diminish of large follicles, (2) occupation of small follicles all over the parenchym of the gland after the surgery. Is this increase in the small follicles attributable to the alteration from large follicle or to a newly developed proliferation? This must be assumed to be newly occurred proliferation of the follicles, since the fibrosis is not remarkable, and small follicle proliferates parenchymatously containing imperfect colloid in their inner space and moreover, there can be observed some follicles which has no colloidal content. Furthermore, it is chracteristic that the conglomeration of these small follicles occupies parechymatously all over the gland, which is apparently different from the proliferation commonly observed in hyperthyroidism. According to these findings, it may be presumed that some follicles proliferated compensatorily taking place in the site of atrophy of the parenchym of the thyroid. Such a diminish in large folliches and an increase in small follicles were also observed in the dogs not treated with insulin as well as in the those treated with it. This change, however, appears shortly after the surgery in the former, while it appears after a long interval in the latter.

7. Somnolent metabolism

As to the rate of metabolism in diabetics, some says accelerated and others declined. OKADA reported that respiratory coefficient diminishes in most cases of serious diabetes.

In normal dogs, respiratory coefficient ranged from 1.04 to 0.70, with a mean of 0.88, while it showed lower rate in completely depancreatized dogs as 0.67 to 0.74, with a mean of 0.72. As to the correlation between insulin doses and the coefficient, it showed small rate irrespective of insulin dose with an exception of a case which shows a slight increase. (Tab. 8)

Tab. 8 Pre-, and posotperative respiratory coefficiency

Dog No.	Insulin dosis u/kg	Before Operat.	After Operat.
2	1	1.04	
10	1	0.79	0.72
12	1	0.95	
24	1	0.70	0.72
13	2	0.98	0.74
17	2	0.79	
18	2	0.88	0.73
22	2	0.92	0.67
14	3	0.98	0.73
15	3	0.85	
Mean		0.88	0.72

IV. DISCUSSION

It is a problem of utmost importance to consider about the action of the thyroid hormone in the glycometabolism, when one discusses over the thyroid function in diabetes, in which the utilization of glucose in the peripheral tissues is assumed to be disturbed.

Thyroid hormone urges the phosphorization of glucose in the intestinal tract and enhances the absorption of glucose. On the other hand, it accelerates the decomposition of glycogen in the liver. In addition, it urges metabolism in the perpheral tissue and oxydation of glucose, enhancing at the same time decomposition of protein and mobilizing protein and fat in the periphery to provide the material for glucose synthesis in the liver.

The action thyroid hormone in diabetes following complete pancreatectomy if considered to work in mobilizing peripheral protein to provide the material for glucose synthesis in the liver, rather than in the process of glucose absorption, that is, it works in the process in which the peripheral protein is altered into amino acid, judging from the fact that the rate of glucose absorption is not so much lowered as to be estimated and moreover, from the mechanism of active absorption of glucose in the intestinal tract. Accordingly it can be conceived that in diabetes due to the total pancreatectomy, the thyroid participates in glycometabolism playing rather an indirect role as a constiruent of anti-insulin system.

In the whole course of the present experiment, attention was paid to improve the utilization of protein, glucose and fat by feeding the dogs with well boiled rice, wheat and fish, what differs from the item of diet in the abroad which is chiefly consisted of raw beef and horse-flesh. In addition, development of fatty liver was fairly prevented by the administration oi fnsulin of suitable dose. Moreover, attentions were paid to lessen the mortality of the operation, and to provide a favorable condition for long survival. In this direction, for instance, the animals were anesthesized with intravenous anesthetics and autonomic nervous system blocking agent was used at the same time in the aim of potential anesthesia, that is, the autonomic nervous system blocking agent was used for its beneficial effect to prevent shock and to depress metabolism of organism and its advantages as it strengthen the effect of barbiturate which does not act as an anodyne, but hypnotics.

As the routine examination of thyroid function, determinations of thyroid ^{131}I uptake, PBI level and basal metabolism are widely carried out. HERTZ, in 1938, first carried out thyroid ^{131}I uptake, assuming it to indicate thyroid function directly. This procedure has become to be carried out more popularly, since he found that radioactive iodine concentrates markedly in the thyroid of animals. It has been assured that radioactive iodine, when injected into an organism, behaves quite similarly to nonradioactive iodine ^{127}I mixing together with it which naturally exsists in the body. That is, radioactive iodine, being taken up into the thyroid, participating in synthesis of thyroid hormone, being secreted into blood streem and being consumed in the peripheral tissues. Accordingly, it is possible to know the behavior of iodine in the body by tracing that of radioactive iodine in it. In hyperthyroidism, thyroid ^{131}I uptake is found to be highly eleveted and PB ^{131}I also. On the contrary, both thyroid ^{131}I uptake and PB ^{131}I are prominently

decreased in hypothyroidism. These findings reveal the fact that thyroid iodine uptake is increased, and synthesis and release of the hormone is enhances in hyperthyroidism and reversed in hypothyroidism. Therefore, PB ^{131}I C. R. corelates well with thyroid function, showing higher level in hyperthyroidism and lower level in hypothyroidism. MARUMOTO reported that six cases out of 11 showed ^{131}I excretion pattern of hyperthyroidism in diabetic, and WERNER also reported constant increase in thyroid ^{131}I uptake in diabetics. On the other hand, INA reported that thyroid ^{131}I uptake and PBI level were found to be decreased, with an increase in excretion of radioactive iodine in diabetics treated with insulin. He assured further in albino rats that thyroid ^{131}I uptake was decreased by an administration with insulin.

Thyroid ^{131}I uptake should be taken into account with blood ^{131}I concentration, since blood ^{131}I concentration together with renal function has much to do with thyroid ^{131}I uptake.

It has been reported concerning PBI that it shows higher level in diabetics than in normal men, which, when treated with insulin, shows a decrease. Blood-plasma protein-bound iodine also reflects thyroid function fairly well, showing high level in hyperthyroidism and reversed in hypothyroidism.

To consider the thyroid function of completely depancreatectomized dogs treated with insulin, taking above mentioned findings into account, it is deemed to be declined, judging from decreased uptake of radioactive iodine, decreased PB ^{131}I C. R. and PBI level, i. e. hypothyroidism.

Here a question, however, arises whether the hypothyroidism is primary one or secondary to pituitary insufficiency. TSH-test was carried out to discriminate whether.

It is widely known from the experiments of CHAIKOFF and BECKER using radioactive iodine that the thyroid function is controlled by the pituitary gland through its thyroid stimulating hormone. A number of attempt to estimate thyroid function using TSH have been tried. SCHNEEBERG, JEFFERIES and others attempted to discriminate primary hypothyroidism from hypothyroidism secondary to pituitary insufficiency by the use of TSH. KEATING conceived the existence of two phases in the process in which TSH acts, that is, first a release cf thyroid hormone and second an increase in thyroid ^{131}I uptake. STANLEY and WOLF pointed out the fact that there can be observed an increase both in PBI level and thyroid ^{131}I uptake and faculty of release and uptake are similarly stimulated by TSH, though there exists a lag phase between uptake and release. In primary hypothyroidism, in which both thyroid ^{131}I uptake and PBI level were estimated to be decreased, there were no change in these two values after the administration cf TSH revealing the findings of atrophy of thyroid gland and degeneration of follicle cells histologically.

As to hypothyroidism secondary to pituitary insufficiency it has been noticed that larger dose of TSH can induce changes in these two values, although usual dose cannot. The thyroid function of completely depancreatized dog is deemed to be declined, observing from a stand point of thyroid reserve to TSH, that is, less increase in thyroid ^{131}I uptake and PBI level compared to those of normal dogs. It is thought to be certain that the cause of hypothyroidism of completely depancreatized dog consists in the pituitary gland,

since it was impossible to observe histological appearance such as monotonous degeneration of epithelial cells in follicles, and in addition, the appearance chiefly consisted of proliferation of small follicles scattered with focal degeneration. It is alreadyas certained experimentally by HASEGAWA that the function of pituitary gland declines when the pancreas is completely removed. Accordingly, it is obviously accepted that the hypothyridoism due to total pancreatectomy has its cause in the pituitary gland, when one considers the fact that there lies so-called feedback mechanism in hypophysis-thyroid system and the pituitary gland and the thyroid perform mutual adjustment to each other through TSH and thyroxin. The decrease in thyroxin secretion should be considered to be an adaptation of organism in the direction to lessen the disturbance of glucose utilization in diabetic, which is due to shortage of insulin following complete pancreatectomy, judfing from the fact that thyroxin promotes the degradation of insulin.

Thus the declined thyroid function gradually restores, with the promotion of glucose utilization following administration of insulin of suitable dose.

V. SUMMARY

Thyroid function of completely depancreatized dog was studied, under the administration of insulin at the dose of 1 to 3 u/kg, and following results were obtained.

1) Thyroid ^{131}I uptake showed a tendency of decrease after the surgery with its lowest level at the 8th week. Some cases showed, however, a slight approach to the level before the operation more than 8 weeks after the surgery.

2) PB ^{131}I C. R. also decreased, as well as thyroid ^{131}I uptake, which showed, although it remained in lowered level, an approach to the preoperative level 8 weeks after the operation.

3) Serum PBI level decreased after the surgery as days went, on, which showed little change maintaining lowered level more than 8 weeks after the surgery.

4) In TSH-test which takes both thyroid ^{131}I uptake and serum PBI level as indication, it was clarified that thyroid reserve declined indicators showing a tendency of an increase after the 8th postoperative week.

5) Weights of thyroid gland decreased after total pancreatectomy.

6) Histological examination revealed an increase in small follicles and a decrease in large follicles in the thyroid gland. These findings are conceived to be a sign of compensation for decline of the thyroid function due to degeneration such as destruction of some follicles.

7) By the determination of somnolent metabolism, postoperative decrease in respiratory coefficient was recognized.

To summarize all these findings, the thyroid function increases temporarily in the early postoperative stadium which decreases as time goes on being accompanied with later recovery, slight as it is, when the completely depancreatized dog is treated with insulin. The appearance of declined thyroid function is considered to be hypothyroidism secondary to pituitary insufficiency.

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和　文　抄　録

「インシユリン」投与下に於ける膵全剔犬の甲状腺機能

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膵全剔犬において，術後「インシュリン」投与量を1～3単位/kg として，甲状腺機能を観察した．即ち

(1)　甲状腺^{131}I 摂取率

術後^{131}I 摂取率は4週目では変動少く，8週目に至り低下する．更に8週目以後では，低下ながら，やゝ上昇の傾向を示す．

(2)　血漿蛋白結合ヨード交換率

術後4週目では低下し，8週目より低下ではあるが，上昇傾向を示す．

(3)　血清蛋白結合沃度

術後日数と共に，PBI値は次第に低下するが，8週目以後では，低値ではあるが，余り変動を認めない．

(4)　TSHテスト

①　甲状腺^{131}I 摂取率を指標とするTSHテスト

②　血清PBIを指標とするTSHテスト

何れの場合も，増加率より見れば，甲状腺予備力は，術後激減するが，8週目より，術前への復帰傾向を示す．

(5)　甲状腺重量

膵全剔後は甲状腺重量は減少する．

(6)　組織学的所見

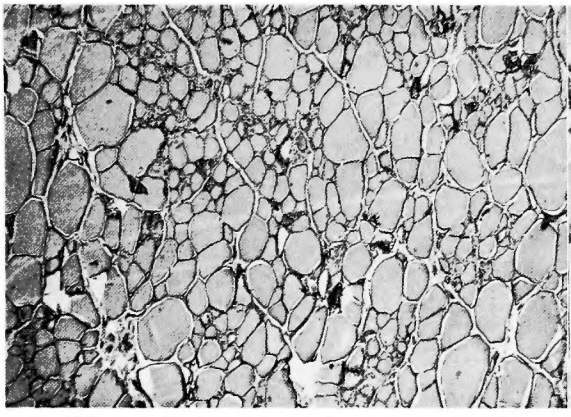
膵全剔後は，大型濾胞の減少，小型濾胞の増加を認める．小型濾胞の増加は，一部濾胞の破壊等の退行性変化による，代償の現れであるが，全体としては機能低下を示す．

(7)　睡眠時代謝

膵全剔後は呼吸高は低下する．

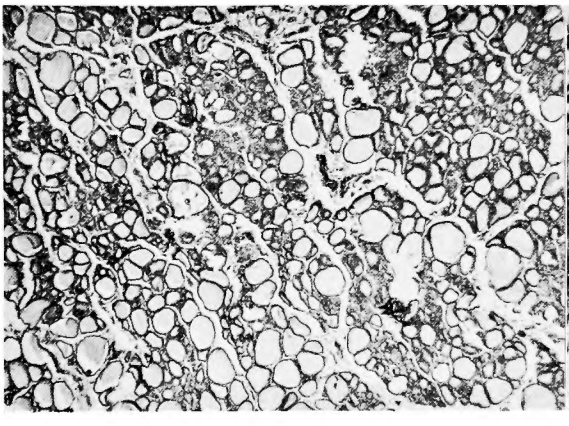
以上を総括すると，膵全剔犬に於いて，「インジュリン」を投与した際には，甲状腺機能は，初期にはやゝ亢進するが，経過と共に低下し，再び低下ながらも，幾らか機能回復の方向へむかう．即ち膵全剔後は甲状腺機能は低下し，膵全剔後の甲状腺機能低下は，下垂体性続発性甲状腺機能低下によるものである．

（尚本論文の要旨は第33，34回日本内分泌学会に於て発表した）



Plat. 1

Plat. 2



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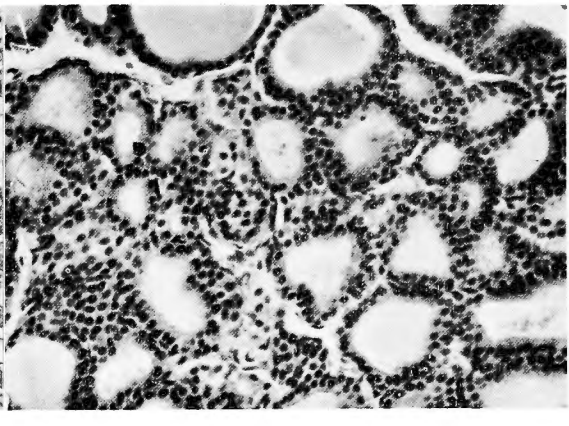

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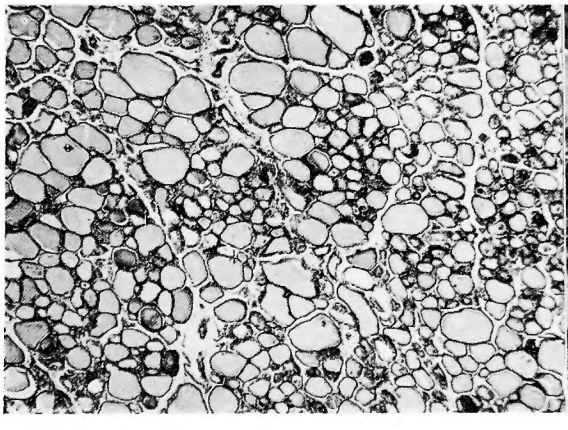

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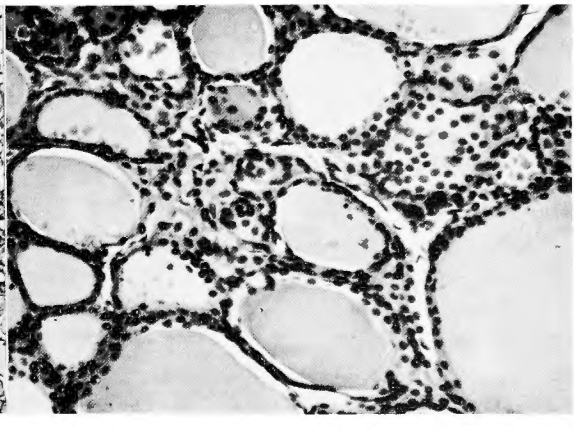

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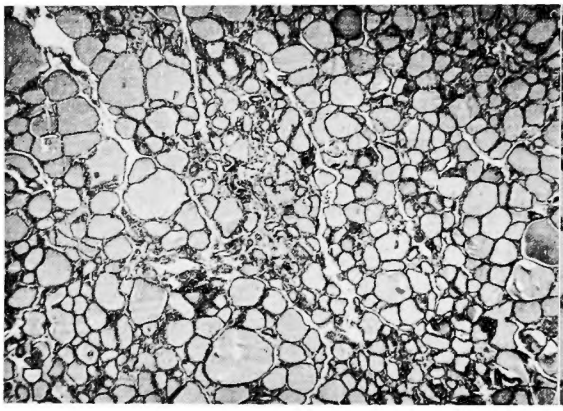

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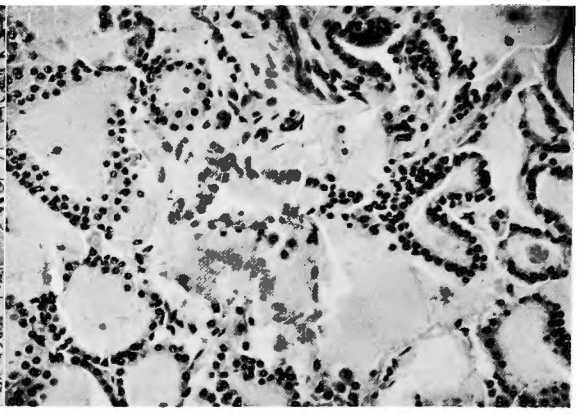
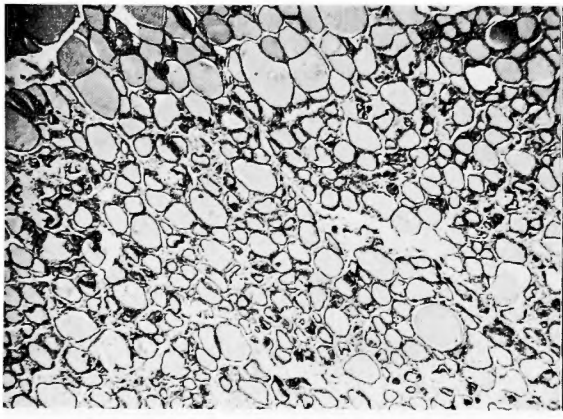
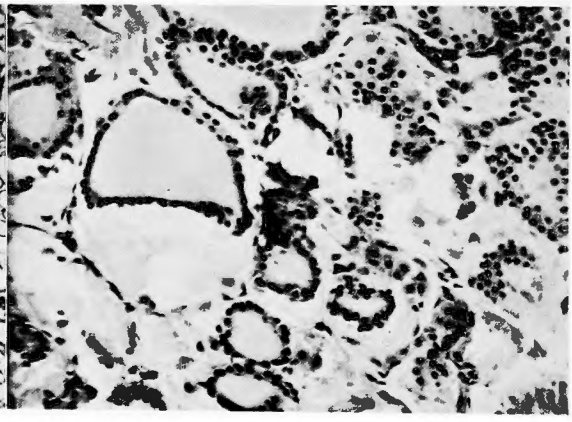


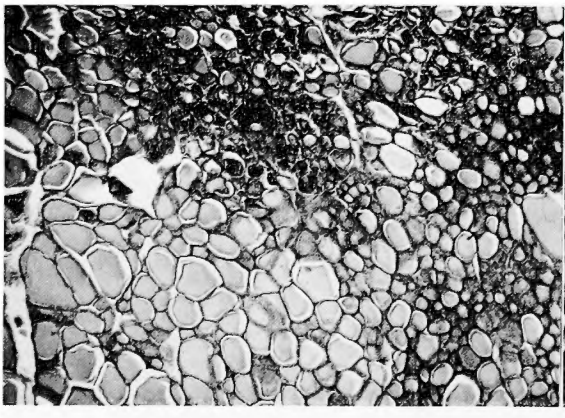
Plat. 8



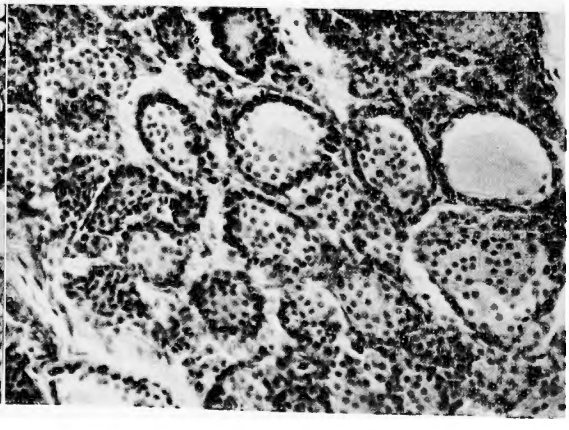
Plat. 9



Plat. 10



Plat. 11



Plat. 12