Effect of the Spleen on the Thyroid Gland (II)

Experimental Studies on the Effect of the Spleen on Thyroid Function by the use of Radioactive Isotope of Iodine

by

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INTRODUCTION

Of all the organ of the body, less is known about the spleen than perhaps any other organ, although the spleen is found practically throughout the animal kingdom.

The endocrinological character of several functions of the spleen is one of the most controvertible problems in the physiology and pathology of this organ. Formerly, the spleen was regarded as one of the endocrine glands along with hypophysis, thyroid gland, suprarenal gland. Several clinical and experimental observations clarified endocrine mechanism of several splenic functions, demonstrating the effects of the spleen on the organs having no direct contact with it. Effects of the spleen on the bone marrow drew the attentions of many investigators, and its suppressive effect on the bone marrow is widely recognized now. Effects of the spleen on serum calcium level, fat metabolism, respiration metabolism, etc., were also investigated and existence of splenic hormone has been presumed. However, unsuccessful investigations on the endocrine substances of the spleen, and the absence of any easily recognizable aberration of the functions of the organism after splenectomy have defended the skeptical attitude toward endocrinological character of the splenic functions.

The interrelations of the spleen with other organs than the bone marrow, particularly with endocrine glands, are far less investigated. Analysis of clinical and experimental materials, however, suggests the possibility of the effect of the spleen on the several functions of endocrine glands, in spite of many contradicitions. The author, having found the fact that the transient thyroidal enlargement by catecholamine injection observed in some patients with splenomegaly but it was not observed after splenectomy in spite of the same injection, and presuming the effect of the spleen on the thyroid, investigated and clarified previously the effect of the spleen, in normal and pathological conditions, on the histology of the thyroid gland both clinically and experimentally. In this paper, the author studied experimentally the effect of the spleen on the functions of the thyroid gland, using radioactive isotope of iodine.

REVIEW OF PERTIENT LITERATURE

Observation demonstrating the existence of correlation between the spleen and the thyroid gland is the earliest of the studies on the correlations between the spleen and the endocrine glands.

Formerly, the splenic function was considered to be compensated by the thyroid

(TIEDMANN, CRÈDE and ZESAS[16]), and CRÈDE (1882)[12] reported enlargement of the thyroid gland after splenectomy.

SAKHAROF (1936)[18], CHRUSTALEW[15], HIRSCHLAFF[15] reported enlargement of the spleen in thyrotoxicosis ; FUJII (1926)[15], GORIZONTOF (1956)[18], MIKHAILOVA (1956)[18] reported enlargement of the spleen of the rat fed with thyroid preparation.

ASHER and his colleagues made many studies of the correlation between the spleen and the thyroid gland. They demonstrated evidences of an antagonistic correlation between these organs, investigating the effect on the organism of splenectomy, thyroidectomy, or of feeding with these organ preparations : 1) DUBOIS (1917)[3] clarified an acceleration of the blood formation of the bone marrow after splenectomy, while a suppression after thyroidectomy. 2) YAMADA (1918)[41] reported a decrease of serum thrombin content after splenectomy, while an increase after thyroidectomy. 3) STREULI (1918)[11] reported an increase of sensitiveness to oxygen deficiency after splenectomy, while a decrease after thyroidectomy. 4) DANOFF (1919)[1] demonstrated an increase of basal metabolism and water metabolism of rat after splenectomy, while a decrease in case of thyroidectomy. 5) MESSERLI (1919)[6] found, under the oxygen deficiency, leukocytosis after splenectomy, while lymphocytosis after thyroidectomy. 6) HAURI (1919)[5] found an increase of the excretion of carbonic acid and water in rabbit after splenectomy, while a decrease after thyroidectomy. 7) According to NAKAO (1925, 1926)[7][8][27], the leukocyte increasing action of sodium nucleide and erythrocyte increasing action of "hemopoietin" disappeared when one of either the spleen or the thyroid gland was removed, but these actions reappeared after the removal of the other. 8) DIETICKER (1927)[2] reported an increase of sensitiveness to low pressure and/or high temperature after splenectomy, while a decrease after thyroidectomy.

TSUJI and his associates also made a various investigations concerning the functions of the spleen and the thyroid gland to demonstrate the existence of an antagonistic correlation between them: 1) IWAI (1927)[22] reported an increase of the thrombocyte in the blood after splenectomy, while a decrease after thyroidectomy. 2) MORI (1927)[26] demonstrated an increased oxydase reaction in various organs after splenectomy, while a decreased one after thyroidectomy. 3) IWAI (1928)[23] clarified an increased osmotic resistance of erythrocyte after splenectomy, while a decreased one after thyroidectomy. 4) NISHIMURA (1928)[28][29] reported an increase in calcium content in the blood in both case of splenectomy and feeding with thyroid preparation. 5) UENO (1928)[40] found an increase of erythrocytes after splenectomy, while a decrease after thyroidectomy. 6) SENNO and MURAO (1928)[33] reported a decrease of liver glycogen after splenectomy, while an increase after thyroidectomy.

FUJIKAWA (1935)[16] found an antagonistic correlation between these organs in regard to the destruction of heterogeneous erythrocyte, the spleen accelerating the destruction while the thyroid suppressing it.

FUJIMURA (1955)[17] demonstrated that the removal of the spleen brought the thyroid and parathyroid gland into a state of dysfunction, taking abnormal salt-fever as an indicator.

The clinical observation that hyperthyroidism is one of the predisposing factors of

BANTI's disease (Ito*) is of great interest.

There are some works on the effects of the spleen in various conditions on the histology of the thyroid gland. According to FUJIKAWA (1935)[16], atrophy of the thyroid followed splenectomy. GASPARINI (1938)[18] found no signs of accelerated function in the thyroids of splenectomized rabbits. FUJIMURA (1955)[17] found, in the thyoids of rabbits 20 days after splenectomy, pictures similar to those found in parenchymatous struma, and markedly congested blood vessels. SUMORI and INOUE (1932) investigated histology of the thyroid gland in hens, and reported that the thyroid was hyperfunctional for 30 days after splenectomy, and hypofunctional thereafter. TAKEUCHI (1950)[36] investigated the histology of the thyroid gland in BANTI's disease, and found that follicles were smaller and colloid was more light-colored than normal, suggesting a slight hypo- or dysfunction, and that interstitial blood vessels were always markedly congested. The author investigated the thyroid glands of the patients with splenomegaly and of the rabbits with experimental splenomegaly, and found markedly congested blood vessels, though any definite findings indicating hyper- or hypofunction were not found.

EXPERIMENT-I

UPTAKE OF I-131 BY THE THYROID GLAND AFTER SPLENECTOMY

EXPERIMENTAL PROCEDURE Normal, young, white rabbits were used throughout the experiments. These rabbits were all from the same stock, weighing 1.5 to 2.0 kilograms, and were approximately of the same age (3 to 5 mos.).

Rabbits were divided into four groups (Control-I, Control-II, Splenectomy-I and Splenectomy-II). The uptake of radioiodine by the thyroid gland was measured in all animals before the operation. 40 days later, the spleen was removed in Splenectomy groups, and only laparotomy was made in Control-II grnup. No operation was made in Control-I group. In Splenectomy-I group. the iodine uptake by the thyroid was measured 30, 150, 270 and 410 days after the operation ; and in Splenectomy-II group, the uptake was measured 50 days after the operation. In Controll-II group, the uptake was measured 30 and 150 days after the operation ; and in Control-I group, the uptake was determined concurrently with the 50- and 150-day-measurement of Splenectomy groups. These procedures are summarized in Table 1.

Table 1 Experimental Procedure (numbers of rabbits in each groups)

	Control-I	Control-II	Splenectomy-I	Splenectomy-II
operation	no operation	laparotomy	splenectomy	splenectomy
preoperative measurement	5	1	8	5
30 days after operation		4	8	
50 days after operation	5			5
150 days after operation	5	4	6	
270 days after operation			4	
410 days after operation			3	

* : reported at General Congress of Clinical Hematological Society. 1964.

For the determination of the iodine uptake, one microcurie per kg of bodyweight of radioiodine was injected into an ear vein of each rabbit. 1, 3, 6, 12, 24 and 48 hours after the injection, the accumulation of radioiodine in the thyroid was determined by direct measurement of gammaradiation from the gland by means of an externally located GEIGER-MÜLLER counter. The results were expressed as per cent of dose in the gland at the time.

$$\text{Uptake} = \frac{A-B}{C-D} \times 100$$

A : thyroid measurement
B : thigh mesurement
C : original dose measurement
D : back ground measurement

In the case of repeated measurements in a rabbit, the time intervals between them were made long enough (70 days or more) ; hence, the repeated injections of minute amount of iodine were considered not to have any serious effects upon the experimental results. (Splenectomy II group was prepared for the 50-days-after-splenectomy uptake determination, for only either one of 30- or 50-days-after-splenectomy determination was possible on the same rabbits.)

RESULTS The iodine collection by the thyroid gland in each experimental group is given in Table 2.

Table 2 Iodine Uptake By The Thyroid Gland(%)

	I. preoperation (22)	II. 30 days after splenectomy(8)	III. 50 days after splenectomy(5)	IV. 150 days after splenectomy (6)
1	13.5 ± 6.6	6.3 ± 3.2	34.9 ± 23.6	32.5 ± 11.7
3	22.5 ± 10.9	12.5 ± 5.0	63.1 ± 22.5	61.7 ± 11.3
6	31.8 ± 13.2	18.3 ± 9.0	80.4 ± 16.4	75.4 ± 15.9
12	39.7 ± 13.7	24.2 ± 12.1	84.1 ± 9.3	77.9 ± 12.0
24	44.6 ± 10.9	33.9 ± 16.0	61.5 ± 11.0	66.1 ± 11.5
48	39.3 ± 9.2	34.6 ± 19.4	51.1 ± 15.1	51.2 ± 1.6
	V. 270 days after splenectomy (4)	VI. 410 days after splenectomy (3)	VII. control (50 days) (5)	VIII. control (150 days) (5)
1	36.9 ± 9.3	30.0 ± 17.1	10.1 ± 2.8	13.5 ± 3.9
3	63.3 ± 12.2	49.1 ± 18.2	17.1 ± 5.9	23.3 ± 8.2
6	76.9 ± 7.2	62.2 ± 15.1	25.1 ± 7.2	34.9 ± 7.6
12	84.7 ± 6.5	72.4 ± 17.5	35.8 ± 8.1	41.8 ± 9.9
24	65.5 ± 2.6	77.1 ± 10.5	40.7 ± 10.9	48.6 ± 6.8
48	57.6 ± 2.7	66.3 ± 11.9	38.2 ± 10.2	40.2 ± 5.2
	IX. 30 days after laparotomy (4)	X. 150 days after laparotomy (4)		
1	10.1 ± 4.0	13.9 ± 4.6		
3	19.0 ± 7.0	23.3 ± 10.1		
6	29.3 ± 6.4	31.2 ± 9.7		
12	39.1 ± 13.2	42.7 ± 10.1		
24	44.4 ± 11.2	45.9 ± 12.0		
48	37.1 ± 10.6	36.6 ± 9.3		

The mean of each group is given with the standard error of the mean.
( ) : numbers of rabbits

Whether the differences among the uptakes of respective groups was significant or not, was statistically investigated. Choosing any two groups, when F, calculated as below, is greater than F_0, statistical fixed number dependent on the sum of rabbits of the two groups, the difference in uptake between the two groups is significant.

$$F = \frac{(\bar{x}-\bar{y})^2}{w^2\left(\frac{1}{N_1}+\frac{1}{N_2}\right)}$$

$$w^2 = \frac{\sum_{i=1}^{N_1}(x_i-\bar{x})^2+\sum_{i=1}^{N_2}(y_i-\bar{y})^2}{N_1+N_2-1}$$

x_i, y_i : measured uptake value
$\bar{x}$, $\bar{y}$: mean uptake value
N_1, N_2 : number of rabbits in respective group

Calculation reveals that F is greater than F_0 in I-II, I-III, I-IV, I-V (cf. Table II); and smaller than F_0 in I-VI, I-VII, I-VIII, I-IX, III-IV, III-V and IV-V. Accordingly it can be said that the uptake was decreased 30 days after splenectomy, and was increased 50, 150, 270 and 410 days after splenectomy, and there was no difference in the degree

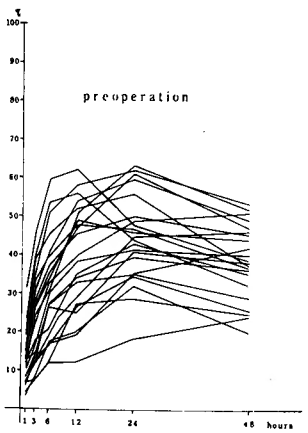
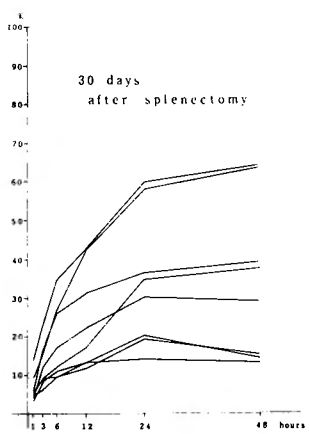


Fig. 1



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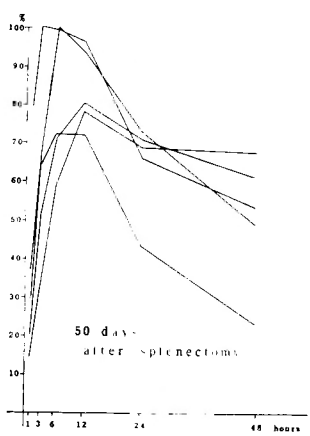

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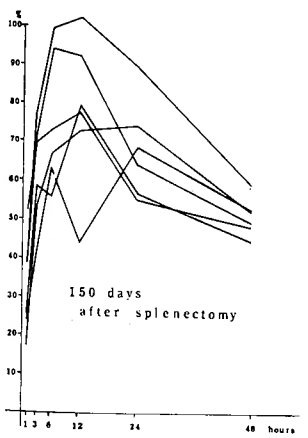

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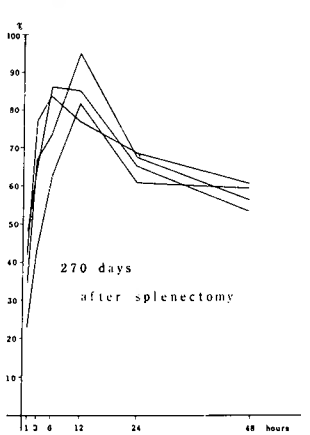

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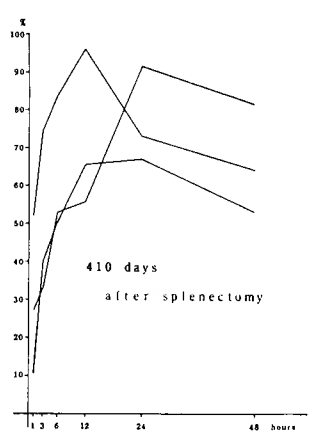

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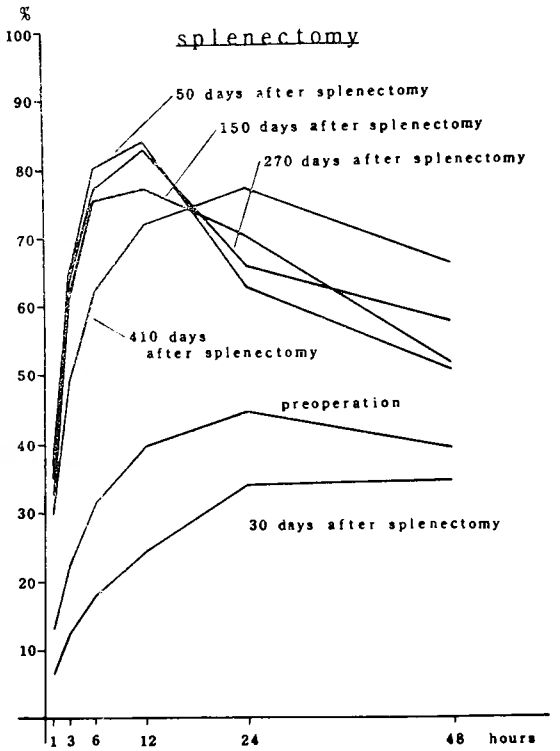

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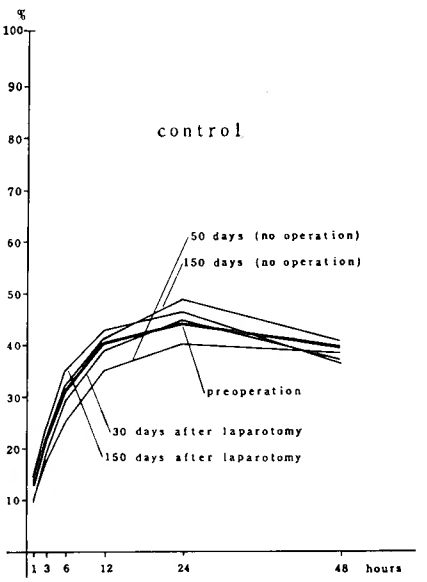


Fig. 8

of increase. (Fig. 1 to Fig. 7) These changes in uptake must be caused by splenectomy, for there were no changes in Control groups. (Fig. 8)

EXPERIMENT-II

UPTAKE OF I-131 BY THE THYROID GLAND AFTER EXPERIMENTAL PRODUCTION OF SPLENOMEGALY

EXPERIMENTAL PROCEDURE For experimental production of splenomegaly, albumin sensitization method (SUZUKI)[60)61)62)63)64)] was used: 2cc per kg of bodyweight of 1% albumin solution (refined albumin "Merk" was dissolved in disinfected physiological saline solution) was intravenously injected daily for 90 days.

Rabbits were divided into two groups (Control and Splenomegaly). The uptake of radioiodine by the thyroid gland was measured in all animals before the sensitization, and then all animals were sensitized with albumin. The sensitization was continued throughout the experiment. In Control group, the spleen was removed before the start of albumin sensitization. In Splenomegaly group, the uptake of radioiodine by the thyroid gland was measured after 20 days' sensitization; and the uptakes of all animals were measured after 90 days' sensitization. Then, in Splenomegaly group, the spleen was removed; all the spleens were swollen, ranging 1.4 to 4.0g, and averaged 2.6g against the normal average of 0.8g. The spleens were examined histologically and showed fibrosis of pulps, thickening of pulp cords, hyperplasia of reticular cells, narrowed venous sinuses; resembling

Table 3 Experimental Procedure (numbers of rabbits in each groups)

	Control	Splenomegaly
preoperative measurement	6	12
operation	splenectomy	no operation
sensitization for 20 days	—	12
sensitization for 90 days	6	7
operation	—	splenectomy
50 days after operation.	—	5

Table 4 Iodine Uptake By The Thyroid Gland (%)

	I. preoperation (18)	II. sensitization for 20 days (12)	III. sensitization for 90 days (7)
1	14.1 ± 6.6	3.6 ± 3.3	37.6 ± 20.8
3	23.9 ± 10.9	6.6 ± 5.7	66.0 ± 21.9
6	34.4 ± 12.2	9.4 ± 8.0	76.5 ± 20.1
12	42.3 ± 11.9	14.3 ± 9.2	79.2 ± 12.5
24	45.1 ± 10.0	18.7 ± 9.9	67.3 ± 12.7
48	39.6 ± 9.0	17.1 ± 9.5	49.2 ± 6.1

	IV. 50 days after removal of swelled spleen (5)	V. sensitization for 90 days after splenectomy (6)
1	53.1 ± 26.4	39.5 ± 23.1
3	70.9 ± 20.1	74.6 ± 30.2
6	77.4 ± 9.7	78.6 ± 18.9
12	70.9 ± 14.0	78.3 ± 12.2
24	66.1 ± 16.6	52.8 ± 13.2
48	44.5 ± 10.7	42.4 ± 10.6

the fingings found in BANTI's disease. The iodine uptake of Splenomegaly group was measured 50 days after the removal of the swelled spleen. These procedures are summarized in Table 3.

RESULTS The iodine collection by the thyroid gland in Experiment-II is given

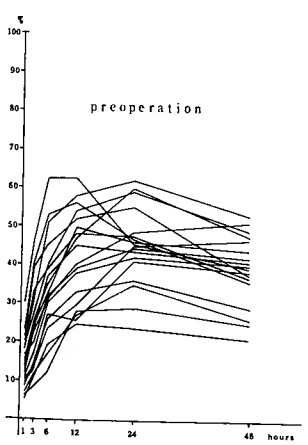


Fig. 9

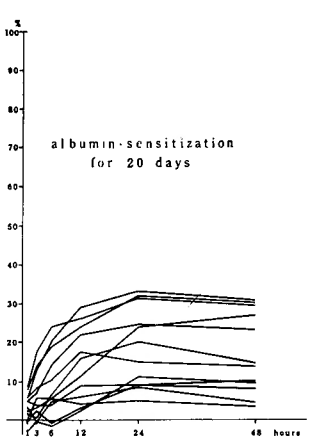
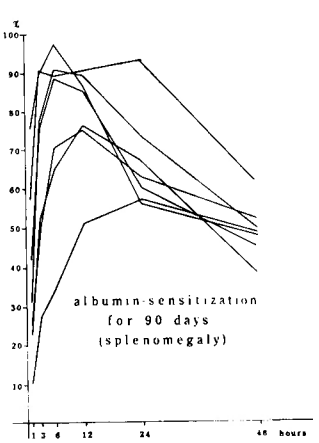


Fig. 10



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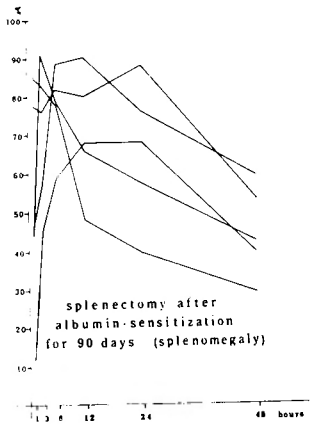

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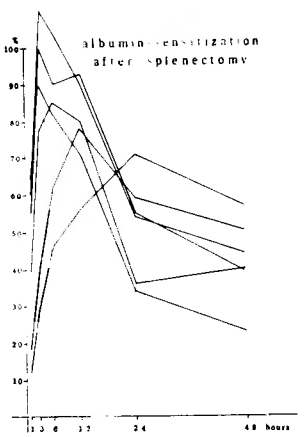

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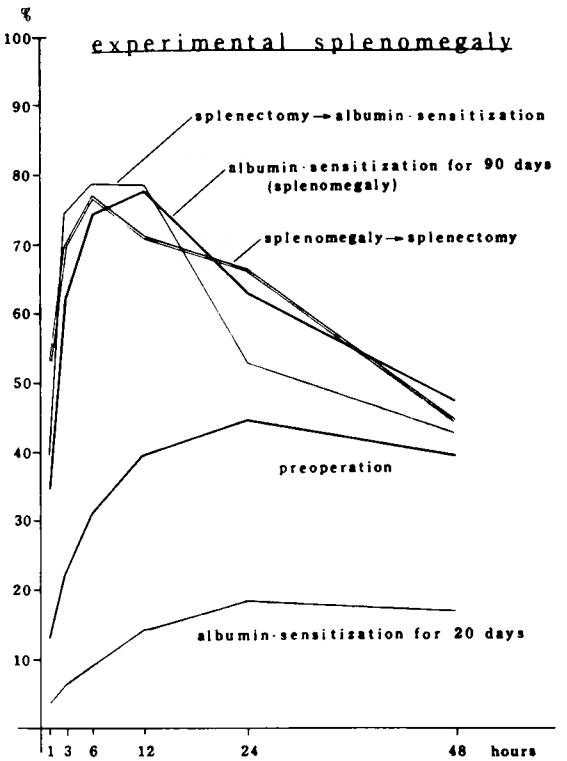

Fig. 14

in Table 4.

Statistical investigation reveals F is greater than F_0 in I-II, I-III, I-IV and I-V (cf. Table IV) ; but smaller in III-IV, and in III-V also. That is, the uptake decreased when sensitized with albumin for 20 days (Fig. 10), but increased when sensitized for 90 days (when splenomegaly was produced) (Fig. 11). The removal of the swelled spleen, however, caused no change in the uptake (Fig. 12). Moreover, it was clarified from the control experiment that the uptake of splenectomized rabbit was increased by the sensitization for 90 days just as much as that of normal rabbit (Fig. 13, Fig. 14). It must be pointed out that the albumin sensitization gave a great effect on the iodine uptake, and the effect of splenomegaly on the iodine uptake might be concealed by the effect of the sensitization.

CONSIDERATION

KRISS[54] reported that the highest thyroidal uptake of radioiodine was obtained within 10 minutes in hyperthyroidism ; TASAKA[57], YOSHIDA[59] and others stated that the difference between hyperthyroidism and normal was most clearly demonstrated in 2- to 6-

hour-uptake ; and YAMAZAKI[58] stated that iodine metabolism in rabbit was carried out faster than in man. Hence, the author determined the uptake 1, 3, 6, 12, 24 and 48 hours after the injection of I-131. In the normal rabbits, 24-hour-uptake was the highest in most of them ; on the other hand, 6- or 12-hour-uptake was the highest in almost all of the hyperfunctional rabbits. No small individual divergence within respective group is observed ; and considerable difference is seen even among normal curves obtained by several investigators. (Table 5)

Table 5 Iodine Uptake By The Thyroid Gland In Normal Rabbits (%)

	Yamazaki[58] (12)	Irie[59] (6)	the author (22)
1	21.8 ± 10.4	—	13.3 ± 6.6
3	29.5 ± 8.8	50.0 ± 14.9	22.5 ± 10.9
6	30.5 ± 8.8	44.3 ± 10.1	31.8 ± 13.2
12	22.0 ± 6.7	39.3 ± 12.9	39.7 ± 13.7
24	15.7 ± 5.6	27.5 ± 15.3	44.6 ± 10.9
48	11.4 ± 6.8	22.7 ± 7.0	39.3 ± 9.2

( ) : numbers of rabbits investigated

Divergence of views among the histological investigations concerning the functional states of the thyroid gland after splenectomy is considered due to, at least partly, the fact that the functional states vary with the time intervals between splenectomy and investigation of the thyroid ; hypofunctional around 30 days after splenectomy and hyperfunctional 50 days or more after.

GELLER[18], FABBRINI[42], MARESCOTTI[42] and others investigated iodine uptake by the thyroid gland, urinary excretion of 17-ketosteroid, 11-oxysteroid, estrogen, gonadotrophin, etc., of splenomegalic patients of various pathogenesis ; and found that the uptake or excretion is decreased in them, but is increased after their splenectomy. It is problematical, however, to regard all splenomegaly as a sign of splenic hyperfunction, considering the result of the Experiment II that the production of splenomegaly and the removal of swelled spleen caused no effect on iodine uptake.

SUZUKI advocated allergic nature of BANTI's disease and reported experimental production of the analogous state to BANTI's disease by albumin sensitization. Iodine uptake of sensitized rabbits were markedly increased, however, while the iodine uptake of splenomegalic patients (including BANTI's disease) were decreased, as mentioned above. Therefore, it must be pointed out that the experimental splenomegaly due to albumin injection is different from BANTI's disease in this point ; and this difference may be of no small significance, when the importance of the endocrinological character of the spleen in BANTI's disease is considered.

HUTCHINSON[42] attributed the impairment of psychosomatic growth of congenital luetic splenomegalic patient to splenomegaly ; FREYMANN[42] and many others reported improvement after splenectomy of impaired psychosomatic growth and sexual insufficiency of splenomegalic patients. These facts suggest the possibility of existence of correlation between the spleen and many endocrine glands. Recently, MARESCOTTI, FABBRINI, PAGNI and others[42] introduced a hypothesis that a special substance from the spleen inactivate

the hormones from hypophysis. From the results of many clinical and experimental investigation, they advocate that an antagonistic correlation exists between the spleen and the suprarenal gland, the sexual glands, the thyroid gland, etc., due to inactivation of trophic hormones of hypophysis by splenic substance.

The result of Experiment-I that iodine uptake by the thyroid increased remarkably over long period of time after splenectomy (after transient decrease) suggests a correlation between the spleen and the thyroid gland; (significance of the transient decrease is a controversial problem). It is observed that the iodine uptake is increased after treatment of thyrotropic hormone, and is greatly decreased following hypophysectomy (LEBLOND and SUE[56], CHAIKOFF[56]); therefore it is conceivable that the correlation is an indirect one through the medium of hypophysis.

SUMMARY

1. Uptake of radioactive iodine by the thyroid gland is decreased 30 days after splenectomy, and is increased remarkably 50, 150, 270 and 410 days after splenectomy.

2. Uptake of radioactive iodine by the thyroid gland is increased in rabbit with experimental splenomegaly produced by albumin sensitization, and removal of the swelled spleen gives no change upon the increased uptake. Sensitization of spleenless rabbit also makes iodine uptake increase, just as much as that of normal rabbit does.

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和文抄録

脾臓と甲状腺の相互関係に関する研究

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脾臓の内分泌学的性格の問題は脾臓の生理及び，病理に於て最も議論の多い問題である．このうち脾臓と骨髄に関する研究は少くないが，内分泌腺との相関に関する研究は遙かに少ない．著者は臨床的観察から脾臓と甲状腺の相関を想定し，臨床的並び実験的研究を行なつて之を立証した．

第一篇　脾腫患者の甲状腺のカテコールアミンによる急性一過性腫脹

1．褐色細胞腫患者の高血圧発作時，初期バセドウ氏病患者の精神興奮時などに急性一過性の甲状腺腫脹が観察されることがあるのは諸家の報告に見られるが，著者は2名の脾腫患者に Frey 氏試験のためカテコールアミンの注射を行なつた際に，同様の甲状腺の一過性腫脹が起るのを観察した．この現象は剔脾後には見られなくなり本現象と脾臓との関連を想定せしめた．そこで脾腫患者と対照にについて本現象を検討したところ，対照例に於ては1例も本現象が見られなかつたのに比し，脾腫患者13例中5例に於て本現象が観察され剔脾後には見られなくなつた．

2．生検によつて脾腫患者の甲状腺組織像を見ると著明な機能亢進又は低下の像は見られなかつたが全例に於て濾胞間毛細管の充盈が見られ対照との間に明らかな差異を認めた．甲状腺腫脹の観察された褐色細胞腫患者の甲状腺に於ても又濾胞間毛細管の充盈が見られることから，この充盈は甲状腺の急性腫脹の発現に意義を有するものと考えられる．

3．アルブミン感作法によつて家兎に実験的脾腫を作成するとその甲状腺にも同じく全例に濾胞間毛細管の充盈が見られた．しかもあらかじめ剔脾を行なつて感作した場合には充盈が見られないので本所見は脾腫に起因すると考えられる．

第二篇　甲状腺 I^{131} 摂取率に及ぼす脾臓の影響

家兎に於て脾臓の甲状腺機能に及ぼす影響を I^{131} 摂取率を用いて検討した．

1．剔脾後30日で摂取率は稍減少を示すが，50，150，270，410日では著明な亢進が見られた．

2．脾種作成の目的でアルブミン感作を行なつたが感作20日では摂取率は稍減少を示し，感作90日，即ち脾腫発現例では著明な亢進が見られた．しかるに脾腫剔除例及びあらかじめ脾剔を行なつて感作した例に於ても同様の亢進が見られ脾腫の影響は明らかではなかつた．

之等の事実は生理学的及び病理学的状態に於ける脾臓が甲状腺に諸種の影響を及ぼしていることを証明するものである．