

EFFECT OF THYROIDECTOMY AND OF THYMECTOMY IN EXPERIMENTAL SYPHILIS OF THE RABBIT.

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In previous papers we have emphasized the importance of the integrity and balance of the system of the glands of internal secretion as one of the factors participating in the reaction of the host to the growth and fate of a transplantable neoplasm of the rabbit (1). This conception was primarily based upon well defined gross and histologic changes in a number of the endocrine glands, and it was felt that there is an essential connection between the growth of the transplanted tumor and certain members of the endocrine system, on the one hand, and the mechanism of animal defense, on the other. Both the thyroid and the thymus glands, in particular, appeared to be profoundly affected, and it was found (2) that the malignancy of the neoplasm was greatly increased in those rabbits in which the thyroid gland was completely removed either before or shortly after inoculation, while a partial thyroidectomy usually resulted in a disease of lessened malignancy. The effect of thymectomy was less clear.

In rabbits infected with *Treponema pallidum*, changes in the glands of internal secretion were also found and these in turn could be related to the mechanism of animal defense as expressed by the clinical manifestations of the disease (3). In order to test further the conception of the importance of this system of organs in the reaction of the host to disease, experiments were undertaken in which the thyroid or thymus glands of rabbits were removed prior to inoculation with *Tr. pallidum*. The results are here reported.

Methods and Material.

Two experiments are reported. The series of animals of the first experiment comprised seven rabbits with a complete thyroidectomy, six with a partial thyroidectomy, and six controls. They were inoculated on January 26, 1923. The opera-

tions were performed 7 and 10 days before inoculation in the case of complete removal of the gland, and 9 days in the case of partial removal. A second series were inoculated on October 29, 1923, and comprised five rabbits with a complete thyroidectomy performed 12 and 13 days previously, five rabbits with partial thyroidectomy performed 14 days previously, six rabbits with complete thymectomy performed 19, 21, and 24 days previously, and eight controls.

All operations were carried out under ether anesthesia. In the case of partial thyroidectomy, one lobe and the isthmus of the gland were removed; while the thymus was totally removed by a transthoracic operation (4, 5). At the end of the experiments, 4 months after inoculation of the first series and 7 months after that of the second, all animals were killed with ether and a complete autopsy performed. A search for thyroid or thymus fragments was made at this time. In two instances a tiny nodule of thyroid tissue was found.

The rabbits were young adult or adult males, matched according to age and breed from a selected stock. They were separately caged and fed a standard diet of hay, oats, and green vegetables.

The strain of *Tr. pallidum* used was the Nichols strain, isolated in 1912, and carried in this laboratory since 1917. Inoculations were made in one testicle with 0.2 cc. of a salt solution emulsion rich in treponemata as determined by dark-field examination. The tissue used for the emulsion was derived from an actively progressing orchitis.

The effect of the various operative procedures was studied in relation to the clinical course of the disease. Each rabbit was examined at frequent intervals and notes made of the general physical condition and disease manifestations. Particular attention was paid to the incubation period, the type and duration of the primary orchitis, the involvement of the uninoculated testicle and of the epididymides and scrota, and the occurrence and course of lesions in remote parts of the body such as the bones and periosteum, the skin and mucous membranes, and the eyes. The duration of the experiments, 4 and 7 months, was determined by the fact that, in the majority of instances after testicular inoculation, healing of syphilitic lesions other than minor residual lesions of the genitalia occurs within 4 months, although certain rabbits may continue to show persistent or recurrent lesions, particularly of the eyes and skin, for longer periods.

The results of the experiments are summarized in a series of tables of which Tables I and III contain abbreviated clinical records of individual animals. A general classification of the grades of infection is given in Table II, with the terms slight, fair, moderate, well marked, and severe. In Tables IV and V we have attempted to indicate graphically the character of the infection of each animal as determined by the lesions developed. Four sizes of solid circles are used. The smallest circle indicates a slight lesion or one of short duration, and in the case of extensions and secondary manifestations, few or transient lesions. The next larger circle indicates a more pronounced lesion or a slight one of long duration or more numerous, more marked, or more lasting extensions and secondaries. The more severe lesions, either of grade, number, or persistence, are designated by the

third and fourth size circles. For convenience, scrotal involvement has been grouped with lesions of the epididymides under the heading of extensions. In the last column of Tables IV and V, the grade of infection of each animal, as shown by the manifestations of the disease, has been designated by a series of one to five plus signs signifying a slight to severe condition.

RESULTS.

The results of the experiments are tabulated in detail so that only the essential features will be referred to.

Considering first the control animals, it is evident that the disease in the first series, Table I, was definitely more severe than in the second, Table III. Such differences in experimental syphilis of the rabbit are not infrequently encountered and, as will be seen later, can definitely influence the results of a particular experiment. Furthermore, well marked individual variations in the disease practically always occur in any single group of five to ten animals. The disease of the control rabbits of the first experiment may be described as of average grade taking into consideration both the genital¹ and the generalized lesions (Tables I and IV). Generalized manifestations occurred in five of the six rabbits (84 per cent) and numbered 25 definite lesions, 5 of the bones and periosteum, 18 of the skin, and 2 of the eyes.

The experiment was ended 4 months after inoculation, at which time active but non-progressive syphilitic lesions of the genitalia were still present in four rabbits and, in addition, the subsiding keratitis in two of these animals could still be seen (Table I). Two of the group had been free from any clinical manifestations for 9 and 14 days respectively. In this control group of six rabbits the infection taken as a whole may be termed moderate to well marked in three, fair in one, and slight in two animals respectively (Table II).

The disease which developed in the animals in which a complete or partial thyroidectomy (Groups A and B, Table I) had been

¹ We have not attempted to separate what might properly be considered true metastatic lesions of the scrota from those which develop as extensions from lesions of the testicle or tunics or from those occurring at the site of needle puncture at the time of testicular inoculation. Some involvement of the epididymis probably always occurs as a direct extension from the testicular process, and frequently the lesions persist after regression and healing of the orchitis. We have included only those instances which were clinically unmistakable.

TABLE I.
Course of Infection. Experiment 1.

Group and No. of rabbit	Incubation period.				Incubation period and No. of lesions in remote sites of the body.				Freedom from lesions.		Postmortem examination.	
	Orchitis.		Scrotal lesions.		Bones and periosteum.	Skin.	Mucous membrane.	Eyes.	Total No.	days	Time after inoculation.	Residual syphilitic lesions.
	Primary.	Metastatic.	Right	Left								
1	10	39							2	0	117	Left orchitis, periorchitis, and epididymitis. Right and left keratitis.
2	14	35				73 (1)			1	15	123	Negative.
3	10	35	73	73	45-66 (8)	45-112 (12)	73-98 (2)	73 (2)	24	0	125	Left orchitis. Right and left keratitis. Lesions of bones and skin.
4	10	35			47-52 (6)	47-68 (28)	68 (1)	73 (2)	37	0	116	Right scrotal lesion.
5	10	32	35	35	45-61 (4)	55 (2)	73 (1)	81 (2)	8	10	122	Negative.
6	10	35	68	68					1	0	123	Right periorchitis. Right scrotal lesion. Left orchitis, periorchitis, and scrotal lesion.
7	10	44							0	24	118	Negative.
	10.5 (av.)	36.4 (av.)			18	43	4	8	73	16.3 (av.)		

B	1	24	55	46									0	20	118	Negative.
	2	21	52	35									1	20	118	"
	3	21	44	61		61	(1)						0	0	123	Right epididymitis?
	4	29	59	39									0	25	123	Negative.
	5	21	59										2	8	119	"
	6	21	61			61	(1)						1	35	116	"
			22.8 (av.)	55.0 (av.)				1		2			1	4	21.6 (av.)	
C	1	10	48										0	9	117	Negative.
	2	24	46	52	83								1	0	123	Right epididymitis. Right keratitis.
	3	10	46	61		55-68	(2)						2	0	123	Right orchitis, periorchitis, and epididymitis. Right scrotal lesion.
	4	14	44	55	89	61	(1)	55-89	(9)				11	0	122	Right orchitis, periorchitis, and epididymitis. Left or- chitis. Left keratitis.
	5	10	44	32	44			55-68	(4)				4	14	119	Negative.
	6	7	41	52		53-68	(2)	55-80	(5)				7	0	116	Right and left epididymitis.
			12.5 (av.)	44.8 (av.)				5	18				2	25	11.5 (av.)	

Group A. Complete thyroidectomy.
 " B. Partial
 " C. Controls.

TABLE II.
Classification of Grade of Infection.

	Complete thyroidectomy.	Partial thyroidectomy.	Complete thymectomy.	Controls.
Experiment 1.				
Severe,	2 (Nos. 3, 4)			1 (No. 4)
Well marked,	1 (No. 5)	1 (No. 5)		2 (Nos. 5, 6)
Moderate,	3 (Nos. 1, 2, 6)	5 (Nos. 1, 2, 3, 4, 6)		1 (No. 3)
Fair,	1 (No. 7)			2 (Nos. 1, 2)
Slight,				
Experiment 2.				
Severe,	1 (No. 1)			1 (No. 8)
Well marked,	2 (Nos. 4, 5)	1 (No. 1)	2 (Nos. 1, 4)	2 (Nos. 4, 7)
Moderate,	2 (Nos. 2, 3)	4 (Nos. 2, 3, 4, 5)	4 (Nos. 2, 3, 5, 6)	5 (Nos. 1, 2, 3, 5, 6)
Fair,	1 (No. 6)			
Slight,				

performed shortly before inoculation differed in many respects from that of the controls. Considering first the complete thyroidectomy group, the disease as a whole was much more marked. The average incubation period of the primary orchitis was 2 days shorter than in the controls, while the metastatic orchitis developed 8 days earlier and the general character of the genital lesions was generally more severe than in the controls.

A most striking difference in the completely thyroidectomized rabbits was in the generalized lesions (Group A, Tables I and IV).

There were 73 secondary lesions among six of the seven animals of the group; that is, twice as many per animal as in the controls. They were distributed as follows: bones and periosteum 18, skin 43, mucous membranes 4, eyes 8. Their time of appearance was generally earlier than in the controls, and, in addition, their duration was longer, as shown by the presence of a number of lesions 4 months after inoculation (Table I, last column).

The general character of lesions in the completely thyroidectomized rabbits was rather peculiar. The primary and metastatic orchitis and many cutaneous granulomata, including those of the scrota, were extensive processes with an unusual degree of boggy induration which gradually became extremely hard. Regression and resolution of all lesions proceeded slowly, and, in the case of the skin granulomata, there was a noticeable tendency toward the persistence of dry, indolent, skin nodules or patches of thickening. Renewed activity of all types of lesions with a return of progressive growth is not infrequently observed in normal rabbits but this characteristic was more noticeable in the thyroidectomized animals and contributed to the longer duration of the clinical manifestations of the disease.

At the end of the experiment, four thyroidectomized rabbits still showed active syphilitic lesions while the residual lesions in the control animals were less marked and were, for the most part, regressing. The relative proportion of the various grades of infection, as seen in Table II, was about the same as in the controls, but in two operated rabbits, Nos. 3 and 4, the disease was very severe. No other rabbit in the entire experiment approached these in the number, variety, and severity of generalized lesions.

The group of partially thyroidectomized rabbits (Table I, Group B) showed a disease picture quite different from that of either the controls or completely thyroidectomized animals in that the manifestations of the infection were of an extremely mild or benign type. The incubation period of both the primary and metastatic orchitis

TABLE III.
Course of Infection. Experiment 2.

Group and No. of rabbit.	Incubation period.				Incubation period and No. of lesions in remote sites of the body.					Postmortem examination.		
	Orchitis.		Scrotal lesions.		Bones and periosteum.	Skin.	Mucous membrane.	Eyes.	Total No.	Freedom from lesions.	Time after inoculation.	
	Primary.	Metastatic.	Right.	Left.								
A												
1	9	39			54-73 (8)		149 (1)	73 (2)	11	29	220	Negative.
2	14	35	44		59-63 (4)		154 (1)	73-86 (2)	7	24	220	"
3	14	38			65 (1)	154 (1)	141-154 (2)		4	0	220	Penis. Anus.
4	14	39	42		59 (1)		167 (1)	80-170 (2)	4	0	220	Right periorchitis and epididymitis. Left periorchitis. Anus.
5	14	38	32	127	54-59 (3)			88 (2)	5	0	220	Necrosis of nasal bone. Right and left periorchitis.
6	9	32	44						0	0	220	Left epididymitis.
	12.3 (av.)	36.8 (av.)			17	1	5	8	31	26.4 (av.)		
B												
1	21	54	28	77	73 (1)	89-127 (6)			7	30	221	Negative.
2	18	50	73						0	115	221	"
3	18								0	122	221	"

4	21	51	59		54	(1)		66-77	(2)	0	97	221	Negative.
5	18									3	115	221	"
	19.2	51.6								10	95.8		
	(av.)	(av.)									(av.)		
C													
1	18	47		63-73	(4)					4	47	224	Negative.
2	9	?								0	87	224	"
3	18	47						89-127	(1)	1	70	224	"
4	18	42		63	(1)	63-98	(3)			4	70	224	"
5	18	59	73							0	119	224	"
6	21	54								0	126	224	"
	17.0	49.8								9	86.5		
	(av.)	(av.)									(av.)		
D													
1	18	42						149	(1)	1	23	219	Negative.
2	14	42								0	114	219	"
3	14	35	59							0	96	219	"
4	14	38				59	(1)			2	96	219	"
5	14	47	73			59	(1)			1	121	219	"
6	32	50	44							1	37	219	"
7	14	?		59-63	(2)					3	97	220	"
8	14	42	77	59-73	(2)	98	(5)			8	83	220	"
	16.7	42.2								16	83.3		
	(av.)	(av.)									(av.)		

Group A. Complete thyroidectomy.
 " B. Partial
 " C. Thymectomy.
 " D. Controls.

was significantly longer (Table I, Group B), and the genital lesions, as a whole, were less marked and of shorter duration than those in the other two groups (Table IV).

The mild character of the infection in these partially thyroidectomized rabbits is particularly well illustrated by the extremely small number of generalized lesions—only four—which occurred in three of the six animals (Tables I and IV). In one rabbit there was a small skin granuloma, and in another, one bone lesion; while in the third animal there was a skin granuloma and a unilateral keratitis. These lesions developed at about the same time as those of the controls but were of relatively short duration and all were healed before the end of the experiment.

There was one rabbit in the partial thyroidectomy group, No. 5, with an infection which has been classified as of fair grade, comparable to that of No. 3 in the controls or of Nos. 1, 2, and 6 in the completely thyroidectomized group, while the disease of the other five rabbits was only of a slight grade (Table II).

In the second experiment the differences in the disease picture of the various groups are somewhat less striking, perhaps because the infection itself was on a lower plane of severity.

This is shown by the longer incubation period of the primary orchitis (Table III), the less pronounced character of this and other genital lesions, and the fewer number of generalized manifestations (Table V). There were 16 secondary lesions distributed as follows: bones and periosteum 5, skin 7, eyes 4. The bone lesions and one of the skin occurred in the usual time, that is 2 months after inoculation, but five skin granulomata developed much later than usual (Rabbit 8), as was also the case with three of the four instances of a keratitis.

This experiment lasted 7 months and at its termination no residual syphilitic lesions in the control rabbits were found clinically or in the gross at postmortem examination. The average time in which there had been no clinical manifestations of the disease was 83 days. In classifying the types of infection shown by these rabbits, one animal, as in the first experiment, No. 8, is graded as having a disease of moderate severity, in two, Nos. 4 and 7, it was fair, while in the remaining five it was of slight degree (Table II).

There were six rabbits from which the thyroid gland had been removed before inoculation. As in the case of Experiment 1, the disease

was again more severe in them than in the controls. The incubation period of the primary and metastatic orchitis was shorter than in the controls, and the genital lesions, as a whole, were more severe (Tables III and V).

TABLE IV.
Character of Infection as Determined by Lesions Developed.
Experiment 1.

Group and No. of rabbit	Genital lesions				Generalized lesions			Grade of infection
	Primary orchitis	Metastatic orchitis and peri-orchitis	Extensions		Skin and mucous membrane	Bones and periosteum	Eyes	
			Scrota	Epididymides				
A	1	●	●		●		●	++
	2	●	●		●		●	++
	3	●	●	●	●	●	●	++++
	4	●	●	●	●	●	●	++++
	5	●	●	●	●	●	●	+++*
	6	●	●	●	●			++
	7	●	●		●			+**
B	1	●	●	●	●			+
	2	●	●	●	●			+
	3	●	●	●	●			+
	4	●	●	●	●			+
	5	●	●	●	●		●	++
	6	●	●	●	●		●	+
C	1	●	●	●			●	+
	2	●	●***	●	?		●	+
	3	●	●	●	●	●	●	++
	4	●	●	●	●	●	●	+++
	5	●	●	●	●	●	●	+++
	6	●	●	●	●	●	●	+++

Group A Complete thyroidectomy
 " B Partial "
 " C Controls
 * Residual, hyperplastic thyroid nodule
 ** Extensive mange and wound abscess
 *** Left testicle castrated 68th day

Generalized lesions developed in five of the six thyroidectomized rabbits (Table III).

There were 17 lesions of the bones and periosteum, 1 of the skin, 5 of the mucous membranes and mucocutaneous borders, and 8 of the eyes, a total of 31 as contrasted with 16 generalized lesions in six of eight controls. The lesions of the bones and periosteum developed at about the same time as those in the normal

animals, but the majority of eye lesions occurred much earlier; that is, within 73 to 88 days after inoculation. There were two lesions of the mucous membrane of the penis and three of the anus developing about 5 months after inoculation, and

TABLE V.
Character of Infection as Determined by Lesions Developed.
Experiment 2.

Group and No. of rabbit	Genital lesions				Generalized lesions			Grade of infection
	Primary orchitis	Metastatic orchitis	Extensions		Skin and mucous membrane	Bones and periosteum	Eyes	
			Scrota	Epididymides				
A 1	●	●		●	●	●	●	+++
A 2	●	●	●	●	●	●	●	++*
A 3	●	●		●	●	●	●	++
A 4	●	●	●	●	●	●	●	+++
A 5	●	●	●	●	●	●	●	+++
A 6	●	●	●	●				+**
B 1	●	●	●	●	●	●		++
B 2	●	●	●	●				+
B 3	●	●	●	●				+
B 4	●	●	●	●				+
B 5	●	●	●	●	●		●	+
C 1	●	●		●		●		++
C 2	●	?		●				+
C 3	●	●		●			●	+
C 4	●	●		●	●	●		++
C 5	●	●	●	●				+
C 6	●	●		●				+
D 1	●	●	●	●			●	+
D 2	●	●	●	●				+
D 3	●	●	●	●				+
D 4	●	●	●	●	●	●		++
D 5	●	●	●	●				+***
D 6	●	●	●	●			●	+
D 7	●	?	●	●		●	●	++
D 8	●	●	●	●	●	●	●	+++

Group A Complete thyroidectomy

" B Partial thyroidectomy

" C Thymectomy

" D Controls

* Residual, pinhead thyroid nodule

** Multiple cutaneous and pulmonary abscesses

*** Multiple pulmonary abscesses

again, as in the thyroidectomized rabbits of the first experiment, these were the only lesions of this class in the entire series. The one instance of cutaneous involvement developed in association with a lesion of the adjacent mucous membrane of the anus.

At the end of the experiment four rabbits showed residual syphilitic lesions, while none were found in any of the other animals of the series (Table III). In Rabbit 3 the regressing lesions of the penis and the anus were still present; the left epididymis of No. 6 showed a slight granulomatous enlargement; in Rabbit 4 there was a residual right and left periorchitis, a right epididymitis, some thickening of the anal mucosa, and a residual necrosis of the nasal bone; in Rabbit 5 there was an inactive bilateral periorchitis.

We have classified the infection of the thyroidectomized rabbits in this experiment as follows: well marked, 1; moderate, 2; fair, 2; and slight, 1, as shown in Table II.

The disease of the five partially thyroidectomized rabbits was, as in the first experiment, of a more benign character than that of the controls.

The primary orchitis was not as severe and the average incubation period was 3 days longer (Tables III and V). Furthermore, the orchitis of all the partially thyroidectomized rabbits was not clinically apparent before 18 to 21 days, while it was definitely so in six of the eight controls within 14 days. The metastatic orchitis in seven of the eight controls developed after an average incubation period of 6 weeks, but among the five partially thyroidectomized rabbits a similar lesion had occurred in only three after 51 days.

Generalized lesions were found in only two of the five rabbits comprising this group, an animal incidence of 40 per cent as compared with an incidence of 75 per cent in the controls (Table III).

There were 10 such lesions, 1 of the bones and periosteum, 7 of the skin, and 2 of the eyes, and 7 of them occurred in one rabbit, No. 1, obviously the least resistant animal of the group. Rabbit 5 had one cutaneous granuloma and a bilateral keratitis which developed in the unusually short time of 2 months after inoculation.

The duration of both the genital and secondary lesions in this group was relatively short, as is shown by the length of time preceding the close of the experiment in which no lesions were found; that is, 30 to 122 days, or an average of 96 days. In the case of the controls this period was 83 days, while it was but 27 days for the only two completely thyroidectomized rabbits which were negative at the conclusion of the experiment.

In classifying the grades of infection of individual animals in the group, as shown in Table II, we have considered the disease of Rabbit 1 as representing a fair infection and that of the remaining four as slight.

The last division in the experiment consists of a group of six rabbits in which the thymus gland had been completely removed prior to inoculation (Table III, Group C). The infection which developed in these animals was, in general, like that of the partially thyroidectomized rabbits, less severe than in the controls, yet with certain differences.

The primary orchitis was of the same order as that of the controls, but the metastatic orchitis developed a week later and was slightly less pronounced (Tables III and V). By referring to Tables III and V it will be seen that the primary orchitis and the epididymitis of the thymectomized and control rabbits were, on the whole, quite similar, but that as regards the metastatic orchitis and scrotal involvement the thymectomized rabbits more nearly resembled the partially thyroidectomized animals.

As concerns generalized lesions, the thymectomized rabbits were also more like the partially thyroidectomized animals.

There was almost the same total number of lesions, that is nine in one and ten in the other; these occurred in two of five partially thyroidectomized and in three of six thymectomized rabbits. The lesions were distributed as follows: bones and periosteum 5, skin 3, eyes 1 (Tables III and V). Their time of appearance, general character, and duration presented no unusual features.

At the conclusion of the experiment all thymectomized animals had been clinically free from syphilitic manifestations for 47 to 126 days, or an average of 87 days. In this respect the group resembles the controls with an average figure of 83 days rather than the partially thyroidectomized animals whose average time was 96 days.

The degree of infection of the individual rabbits of the group has been classified as follows: fair, 2; slight, 4; as shown in Table II. This grouping resembles that of the partially thyroidectomized rabbits.

DISCUSSION.

The experiments reported indicate that, in rabbits, surgical removal of the whole or a part of the thyroid gland or of the entire thymus gland

shortly before inoculation with *Tr. pallidum* is followed by well defined differences in the clinical manifestations of the disease. In the case of complete thyroidectomy, the effect was, in general, one of increased severity as manifested especially by the shortened incubation period and pronounced grade of both the primary and metastatic orchitis, the much higher incidence of generalized lesions, and the distinct tendency for all lesions to be more enduring than in the control animals or, it may be added, than is ordinarily the case in normal rabbits. Partial thyroidectomy, on the other hand, resulted in a disease that was generally less severe than that of the controls as shown by the milder character of the primary and metastatic orchitis but especially by the low incidence of generalized manifestations and by the relatively short duration of all the lesions. These contrasting effects of complete and partial thyroidectomy occurred in both experiments, although, as has been pointed out, they were more marked in one than in the other.

It is not possible to speak so definitely about the effect induced by ablation of the thymus since it was studied in but one experiment and, as it happened, the less favorable one for a demonstration. The disease which developed in the group of rabbits with a complete thymectomy was of a mild type, much less severe than in the group of completely thyroidectomized animals and, on the whole, somewhat less so than that of the controls. This was particularly evident in the metastatic lesions of the genitalia and the number, incidence, and distribution of generalized manifestations. In many respects the general plane or grade of infection was similar to that of the group of partially thyroidectomized rabbits.

Because of the variations in the character of syphilitic lesions shown by individual animals in any series of five to ten rabbits, we have discussed the effects induced by various surgical procedures on a group basis. However, the disease manifestations in certain rabbits were of particular interest.

In the first set of completely thyroidectomized rabbits there were two animals (Table I, Group A, Rabbits 3 and 4) and in the second set there was one (Table II, Group A, Rabbit 1) in which the disease was considerably more severe than in any other animal of either series.

In the second experiment, there was one rabbit (Table III, Group B, Rabbit 1)

in which partial thyroidectomy was followed by more marked disease manifestations than in the other rabbits of this group. A somewhat similar instance is that of Rabbit 4 in the thymectomy group (Table III, Group C). In both animals there was but one bone lesion, a fact which would indicate that at this time the resistance of the host was on a comparatively high level. Subsequently, however, this level was lowered sufficiently to allow the development of skin granulomata, six in the case of the partially thyroidectomized and three in the thymectomized rabbit. Since no further lesions developed it may be presumed that the plane of resistance again was raised, probably in connection with the occurrence and healing of the skin lesions. The disease picture of these two rabbits should be compared with the similar one of Control Rabbit 8 (Table III, Group D). In this animal there were two lesions of the bone and five of the skin but the resistance of this animal, unlike that of the partially thyroidectomized and thymectomized rabbits mentioned above, was not sufficient to prevent the subsequent development of a keratitis. In other words, the least resistant control animal was less resistant than the least resistant partially thyroidectomized and thymectomized rabbits.

There are several phases of this work which are significant from the standpoint of the biology of syphilitic infections. It is evident that the general character or severity of the disease at the time of the experiment is a factor which may influence such effects as are induced by the various operative procedures employed. Thus, when the severity of the disease is of average grade, as in the first experiment, the effect of complete or partial removal of the thyroid is striking, as is shown graphically in Table IV. Syphilitic lesions were much more pronounced in the group of rabbits in which the thyroid had been completely removed than in the control group. The effect of a partial thyroidectomy, on the other hand, was in the opposite direction, the disease being less severe than in the controls. When, however, the disease was pursuing a relatively mild course with fewer generalized lesions, as in the second experiment, the effects of complete or partial thyroidectomy were less conspicuous (Table V).

If one considers experimental syphilis of the rabbit as largely determined, in its manifestations, by the reaction and resistance of the host, either natural or acquired, then it is evident that animal resistance was on a higher plane in the second experiment than in the first. In such rabbits as those of the second experiment, factors which would operate toward a depreciation of resistance might not be able to produce this effect to the degree that would be possible under inherent or so called "natural" conditions of lower resistance. On the other

hand, factors which tend to increase the forces of defense or to render them more efficacious might be reflected in a disease little if at all milder than that which would actually develop in such initially resistant animals.

In this discussion of the relationship between the manifestations of the disease and the resistance of the experimental animal, one other point may be briefly referred to. It has been shown that the occurrence of various manifestations of the disease as well as their severity and duration bear a definite relationship to one another (6). Lesions of the eyes occur most frequently in cases of severe syphilis or in animals in which previous lesions have been comparatively slight or of relatively short duration; they rarely occur in animals that show a prompt and vigorous reaction. It may be added that eye lesions are usually terminal events in the manifestations of the disease, and that the most common type is a keratitis. Extensive cutaneous involvement, save in cases of malignant syphilis, is usually associated with minor bone lesions or none, and this condition has been interpreted upon the basis that the resistance of the animals, which was sufficiently high following the primary orchitis to prevent the development of bone lesions, was not sufficient to afford protection to the skin. The occurrence of bone lesions, however, indicates that the resistance of the animal is not high at the time of their development. If no cutaneous lesions develop, a sufficient resistance may be assumed to have taken place in association with the development and course of the preceding lesions.

The primary reaction of the completely thyroidectomized rabbits was unusually prompt and vigorous, but it was followed by numerous secondary manifestations including a large proportion of eye lesions. There were eight instances of eye involvement among four animals of each experiment. Among the partially thyroidectomized rabbits, on the other hand, although the primary reaction was, in general, slight, the subsequent course of events was contrary to what might have been expected in normal animals. In the first experiment there was only one lesion of the bones and two of the skin, but instead of a fair number of eye lesions subsequently only one developed, indicating the persistence of a high state of resistance. In the second experiment there was again one bone lesion but seven of the skin, six of which

occurred in one animal,—the two instances of eye lesions developed in the animal that had previously a single granuloma of the skin. While the proportion of eye lesions in the partially thyroidectomized rabbits of the second experiment is practically the same as in the controls, they were distributed in the control group among four animals, an animal incidence of 50 per cent, whereas in the operated group they were limited to one, an animal incidence of 20 per cent.

In the thymectomized group, somewhat different conditions prevailed. The primary reaction had a closer resemblance to that of the controls than to that of the partially thyroidectomized rabbits, but the generalized manifestations were less marked especially as regards animal incidence. However, there was only a single instance of eye involvement in the thymectomized group.

The percentages for the proportion of eye lesions which developed in the several groups of both experiments, figured upon a basis of possible numbers, is as follows: complete thyroidectomy, 61.5 per cent; partial thyroidectomy, 13.6 per cent; thymectomy, 8.3 per cent; controls, 21.4 per cent. In other words, a high proportion of eye lesions in a group of animals with other syphilitic lesions of considerable severity indicates a state of low resistance, while few eye lesions in rabbits with other manifestations of a minor character indicates a high level of resistance.

It is significant that the operative procedures employed did not produce identical effects in every rabbit of a series; that is, individual variations in the clinical manifestations of the disease occurred as in normal animals. It would appear, therefore, that our interference with the thyroid or thymus glands merely altered the reaction of the host on whatever plane or in whatever state it happened to be. From one standpoint the most outspoken effect was obtained with complete removal of the thyroid. This tended in the direction of lowered resistance resulting in a more severe disease. In the case of a malignant neoplasm with which we have worked (2) this effect practically always occurred and was very striking. The less constant effects in syphilitic infections are probably to be explained by the difference in type of the two diseases. In normal rabbits the neoplastic disease is acute or subacute and a certain proportion of deaths occur from widespread metastatic involvement as early as 3 to 4 weeks after

inoculation; while experimental syphilis of the rabbit is essentially a chronic condition, in which secondary lesions in remote parts of the body do not usually occur for about 2 months and which, in the great majority of cases, tends toward complete recovery within 4 to 6 months. Thus, in the case of experimental syphilis there is an opportunity for physiological readjustments between the time of inoculation and the development of generalized lesions which is not present in the case of the tumor. If, on the other hand, such readjustments or compensations are not forthcoming in the case of a syphilitic infection, the more marked generalized manifestations of this disease are comparable to the higher incidence and widespread distribution of metastases seen in the malignant disease of thyroidectomized rabbits. That the factor of time enters in is brought out by the character of the primary and metastatic orchitis, which in both of the experiments here under consideration were more pronounced in the completely thyroidectomized groups than in the controls.

There is some indication that even individual animal variation may have been influenced to some extent by our procedures. The infection was in no instance more than of slight or fair grade in the instances of partial thyroidectomy and perhaps also in those of complete thymectomy, whereas in the controls of the first experiment half of the rabbits had a moderate or well marked infection and in the second experiment there was one such instance (Table II). While it is not impossible that all the rabbits in the partially thyroidectomized and thymectomized groups were naturally of high resistance, the chances are that at least one in each group was less resistant than the others and if not interfered with would have developed a moderate or well marked grade of infection.

It would appear from these experiments that, in the rabbit, surgical removal of the thyroid and of the thymus is followed by alterations in the clinical manifestations of experimental syphilis. We interpret such alterations as a consequence of changes in the mechanism of the host's reaction or resistance to the infection. From this point of view the experiments furnish additional evidence in support of the conception referred to in the beginning of this paper, that the integrity and balance of the system of glands of internal secretion play an important part in the reaction of the host to disease conditions.

SUMMARY AND CONCLUSIONS.

Experiments are described in which the thyroid or thymus gland of rabbits was removed prior to inoculation of the animals with *Tr. pallidum*. The effect of these procedures is described from the standpoint of the manifestations of the disease. After complete thyroidectomy, the disease was considerably more severe than in the controls and very markedly so in certain instances. Partial thyroidectomy, on the other hand, resulted in a milder disease than that of the controls. The effect of complete thymectomy was less pronounced than that of either complete or partial thyroidectomy, but, in general, the syphilis resembled that in partially thyroidectomized animals.

These effects are discussed in relation to the host's reaction and resistance to experimental syphilis and the conclusion was reached that the integrity and balance of the glands of internal secretion play an important rôle in the mechanism of defense against this infection.

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