

## THE HISTOLOGICAL CHANGES IN THE THYROID GLAND OF THE RABBIT FOLLOWING LOBECTOMY.\*

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PLATE 2.

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Since the observations reported by Reverdin and Reverdin (1) and Kocher (2) that total thyroidectomy produced symptoms of operative myxedema or cachexia strumipriva many observers have studied the effect of total and partial thyroidectomy in animals. Wagner (3) performed lobectomy in a dog and in a cat and stated that the remaining lobe increased in size. Fuhr (4), who removed the remaining lobe from 8 to 41 days after the first operation, was unable to confirm this, but Horsley (5) found that after removal of one lobe the other may be four or five times its normal size 160 days later. The cells in the hypertrophied lobe were increased in size and there was plication of the acinus wall while the colloid became less solid. Von Eiselsberg (6) removed one lobe and 3 to 15 days later removed the other, but says he found no naked eye appearance of hypertrophy. In two cases in which the remaining lobe was not removed till 21 and 115 days after the first lobe had been excised he states that he got no evidence of hypertrophy. Halsted (7) carried out a very extensive series of investigations on hypertrophy of the thyroid following partial thyroidectomy. Most of these experiments were of a piecemeal nature, the amount of thyroid tissue being gradually reduced at successive operations. He, however, carried out a number of experiments in which one lobe was excised and the other examined at periods varying from 3 hours to 132 days. No change was observed as a rule before the 22nd day, after which all the glands examined were abnormal. Previous to this in only four experiments was there evidence of early hyperplasia. In one of these the hyperplasia was seen after 7 days, in another after 15 days, and in two others after 19 days. The histological changes which indicated hypertrophy were, increase in size of the epithelium, cellular involution into the vesicles, and thin vacuolated colloid. The changes which were observed in these experiments seemed to bear no relation to the quantity of tissue removed. In a later communication Halsted (8) states that he repeated these experiments under strictly antiseptic precautions in two dogs and got negative results. Under his direction Hunnicutt (9)

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carried out a further series of experiments and found no evidence of hypertrophy. In most, although not all, of these experiments iodine had, however, been used as a skin antiseptic. Marine and his coworkers (10) confirmed Halsted's original work and found that there was a definite relation between iodine content and hypertrophy. They also showed that iodine administration could prevent hypertrophy taking place and also cause reversion of a hypertrophied gland to one of a colloid type. In view of Hunnicutt's findings Marine repeated his earlier work but obtained the same results as before. He thinks that the negative results were due to traces of iodine (11). Loeb (12) performed a series of experiments on guinea pigs in which he excised one lobe and studied the histological changes in the other at periods varying from  $4\frac{1}{2}$  days to 4 months. He found no evidence of definite hypertrophy, but changes were present, especially in the later stages which he thought represented the early stages of hypertrophy.

The present investigation was undertaken with a view to studying the influence which the innervation of the thyroid played in the changes which took place in the gland following lobectomy. The effects of hemithyroidectomy on the remaining lobe were first studied. Experiments were then performed in which the same procedure was adopted and in addition the different nerves to the remaining lobe were divided. The right lobe was excised in every instance. In all these experiments only male rabbits were used and the rabbits were kept on a diet of raw cabbage for a short time before the experiment and throughout the period of observation. The operative technique was similar to that described in a companion paper, particular care being taken to avoid the animals obtaining a supply of iodine either at the operation or during the experiment. The operations were performed under ether anesthesia. All the wounds healed without suppuration. The animals were killed at varying intervals of time following the operation and the tissues were fixed and stained as described in our other paper.

Although operative interference in the region of the neck had been demonstrated in previous experiments not to give rise to changes in the thyroid gland it was thought wise to perform a control experiment in which only a small portion of the thyroid gland was removed, in order to see whether interference with the thyroid itself altered the histological picture. The animal was killed 7 days later but no histological difference could be detected between the two lobes, in marked contrast to the changes observed at the end of the same period in the experiments described below.

*The Effect of Excision of the Right Lobe on the Histology of the Left Lobe.*

This series consisted of five experiments and the animals were killed at periods varying from 2 days to 3 months after the operation. The structure of the lobe removed by operation was compared with that of the lobe removed at the completion of the experiment, and the findings are described in Table I. The microscopic appearance of the normal lobe varied in different animals in a manner similar to that described in our other paper. These experiments showed that lobectomy was followed by a series of histological changes in the remaining lobes. 2 days after the removal of the right lobe the vesicles of the left lobe were slightly increased in size, its colloid more vacuolated, and the epithelial cells slightly larger. After 4 days the vesicles were increased in size and contained more colloid which stained moderately well and was not vacuolated (Fig. 1). At the end of 7 days the vesicles were distended with deeply staining colloid and the glandular cells tended to be flattened (Fig. 2). After the lapse of 3 months the histological picture of the left lobe resembled that of the lobe previously removed. The vesicles were no longer distended with colloid but in some cases contained less than those of the right lobe while the glandular cells were cuboidal and somewhat larger (Fig. 3). The remaining lobe had increased in weight and this was presumably due to an increase in the number of vesicles.

*The Effect of Nerve Division on the Histological Changes after Lobectomy.*

This series consisted of five experiments in which a right hemithyroidectomy was performed and at the same time various nerves on the left side divided. In three experiments the left vagus was divided above the origin of the superior laryngeal nerve, while in the remaining two, the left sympathetic cord was cut as low in the neck as possible. The rabbits were killed at periods varying from 7 days to 4 months and the histological changes which took place are shown in Table II which gives the protocols of the experiments. The histological appearance, both in the experiments in which the vagus was cut and in those in which the sympathetic had been divided, was similar in every respect to that seen at a corresponding time when the nerves were intact.

TABLE

Experiment No.	Time killed after lobectomy.	Weight before lobectomy.	Weight when killed.	Vesicles.			
				Size.		Shape.	
				Right.	Left.	Right.	Left.
21	2	1450	1485	Small and regular.	Slightly larger.	Regular.	Same.
22	4	1495	1495	“ “	Many large.	“	Slightly regular
23	7	2100	1930	Medium and regular.	Much larger.	“	Same.
24	90	1620	1830	Irregular; many large.	Same.	Large, irregular.	“
25	45	1400	1240	Medium and regular.	“	Regular.	“

TABLE

Experiment No.	Time killed after operation.	Weight before operation.	Weight when killed.	Vesicles.			
				Size.		Shape.	
				Right.	Left.	Right.	Left.
Left vagus divide							
27	7	1720	1180	Irregular; some large.	Much larger.	Slightly irregular.	More regular.
28	30	1970	1750	Irregular; most very large.	Much smaller.	Regular.	Slightly irregular.
29	120	1600	2000	Medium.	Same.	“	Same.
Left sympathetic cord							
30	7	2050	1855	Small.	Very large.	Regular.	Irregular.
31	120	1920	2100	Small a few medium.	Same.	“	Same.

		Colloid.		Vacuolation.		Cells.		Cellular involution.	
Amount.		Staining.							
t.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	Right.	Left.
r.	Slightly increased.	Faint.	Same.	Slight.	More marked.	Cuboidal.	Slightly larger.	Absent.	Absent.
	Increased.	"	"	"	Absent.	"	Same.	"	"
r.	Much increased.	Good.	Darker.	Moderate.	Increased.	"	Flat.	"	"
	Less.	"	Slightly fainter.	Absent.	Slight.	Cells flat in large vesicles; others cuboidal.	Columnar.	At a few points there was slight cell involution into vesicles.	Same.
	Same.	"	Same.	Slight.	Same.	Cuboidal.	Slightly larger.	Absent.	Absent.

II.

		Colloid.		Vacuolation.		Cells.		Cellular involution.		Remarks.
Amount.		Staining.								
t.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	

above superior laryngeal.

r.	Increased.	Good.	Same.	Marked.	Same.	Cuboidal.	Flat.	Absent.	Absent.	Marked inspiratory stridor.
	Less.	"	"	A few large vacuoles.	Absent.	Flat.	Cuboidal.	"	"	
r.	Slightly less.	Fairly good.	"	Marked.	Less marked.	Cuboidal.	Larger.	"	"	

divided low in neck.

l.	Large.	Faint.	Same.	Slight.	Slightly increased.	Cuboidal.	Flat.	Absent.	Absent.	Left lobe showed cellular projections into some vesicles.
oder-e.	Same.	Good.	"	Moderate.	Same.	"	Same.	"	"	

## DISCUSSION.

The fact that signs of hyperplasia are present in the remaining lobe 3 months after one lobe has been removed has been frequently observed, but the change which we observed during the first 2 weeks has not been reported by other authors. Few observations have been made, however, at an early date after lobectomy, as most investigators have been interested in compensatory hypertrophy of the gland and not in the early changes. Therefore they did not remove the second lobe until a long time after lobectomy had been performed. The changes which took place at this time are not easy to explain. We do not think that they were due to the animals having obtained a supply of iodine, as we carefully avoided this possibility both during and after the operation. They also do not appear to be a reaction to operation on the neck since such changes were not present in a series of experiments which we performed in which the nerves only were divided, nor in the control experiment in which only a portion of one lobe was removed. The fact that 2 days after the operation the remaining lobe showed a slight increase in size of the vesicles with more marked vacuolation of the colloid and a slight increase in size of the cells lining the vesicles probably indicated an increase in activity. The appearance of the gland at the end of a week was similar to that of a colloid gland, which Marine considers to be the resting state of the thyroid following hyperactivity and the nearest approach to normal which can take place in a gland which has been hyperactive. No studies of basal metabolism were made which would indicate if there had been a primary state of hyperactivity followed by a resting state. The iodine content was not estimated so that we cannot say definitely that the glands at the end of 7 days were of a true colloid nature. It would, therefore, be impossible to venture a definite explanation. We consider it possible, however, that the sudden demand on the thyroid resulting from hemithyroidectomy has caused the thyroid cells to hyperfunction. At the end of 7 days, the demand having been satisfied, it has assumed a resting stage. Thereafter compensatory hypertrophy has gradually become established by an increase in the number of vesicles with a resumption of the normal histological picture.

The changes which occurred were uninfluenced by division of the nerves which pass to the remaining lobe so that the experiments lend no support to the view that the function of the thyroid is controlled by nervous influences.

#### CONCLUSIONS.

1. In a series of rabbits the changes which took place in the histology of the left lobe of the thyroid gland after excision of the right lobe have been studied at varied intervals of time. 2 days after the removal of one lobe the other lobe showed a slightly increased colloid content, an increased vacuolation of the colloid, and a slight increase in the size of the epithelial cells. At the end of a week the vesicles were greatly increased in size, distended with colloid, and the epithelial cells were flattened, while after 3 to 4 months signs of compensatory hypertrophy were present.

2. The changes observed were uninfluenced by division of the vagus or cervical sympathetic.

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## EXPLANATION OF PLATE 2.

- FIG. 1. Experiment 22. Right lobe excised; left lobe 4 days later.  
FIG. 2. Experiment 23. Right lobe excised; left lobe 7 days later.  
FIG. 3. Experiment 24. Right lobe excised; left lobe 90 days later.



Right lobe.

Left lobe.

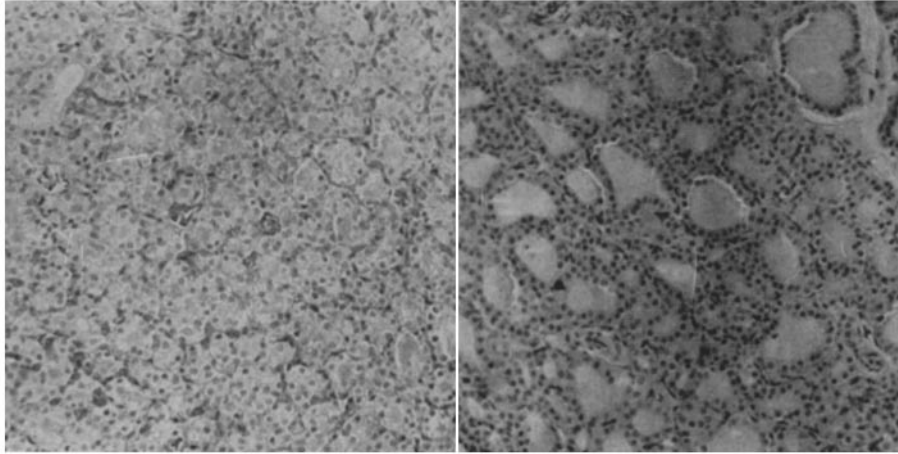


FIG. 1.

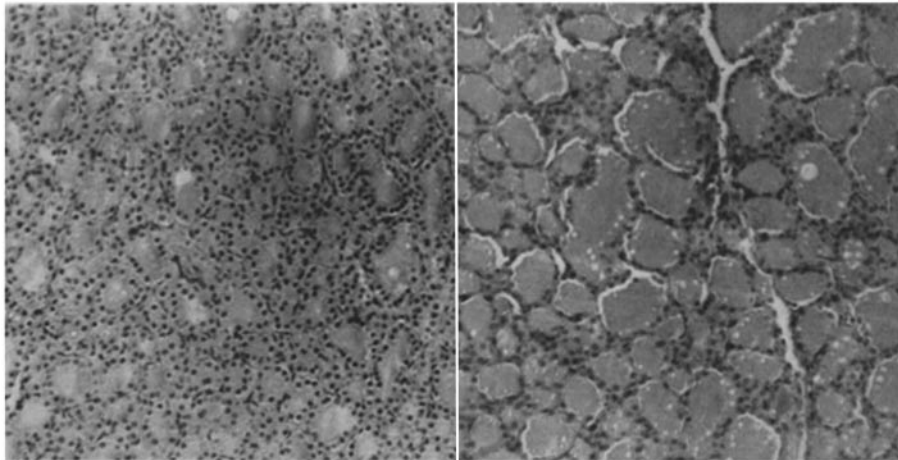


FIG. 2.

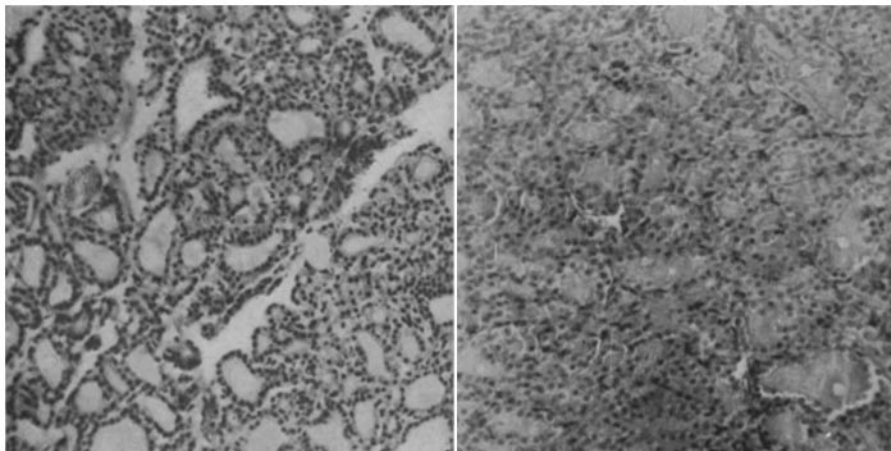


FIG. 3.

(Crawford and Hartley: Thyroid gland after lobectomy.)