THE PHENOMENON OF REGENERATION AND HYPERTROPHY IN THE THYROID GLAND FOLLOWING ITS INJURY

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In the last ten years a number of studies have been published concerning regeneration in the thyroid gland as related to its functional state and to more general physiological conditions [2-6, 9, 11]. Special attention has been paid to the relationship between compensatory hypertrophy and true regeneration in this organ [6-8]. Earlier we have described the variation in capacity for restoration of thyroid parenchyma depending on a number of physiological conditions and on the state of the thyroid gland itself [2, 3]. We proposed that the level of thyroid hormone in the organism is of vital importance for the appearance of compensatory hypertrophy or regeneration in the remaining part of the gland. The stimulating effect of thyroid hormone on various restorative processes is well known [2, 10]. One may admit that preservation of some small fragment of thyroid tissue evokes a significant deficit of hormone in the organism and this in itself may be the basis for compensatory increase in the function of the remaining part of the gland.

To elucidate the correlation between thyroid hypertrophy and regeneration it is necessary to compensate experimentally for the hormone deficit produced by partial thyroidectomy by supplying thyroid from without.

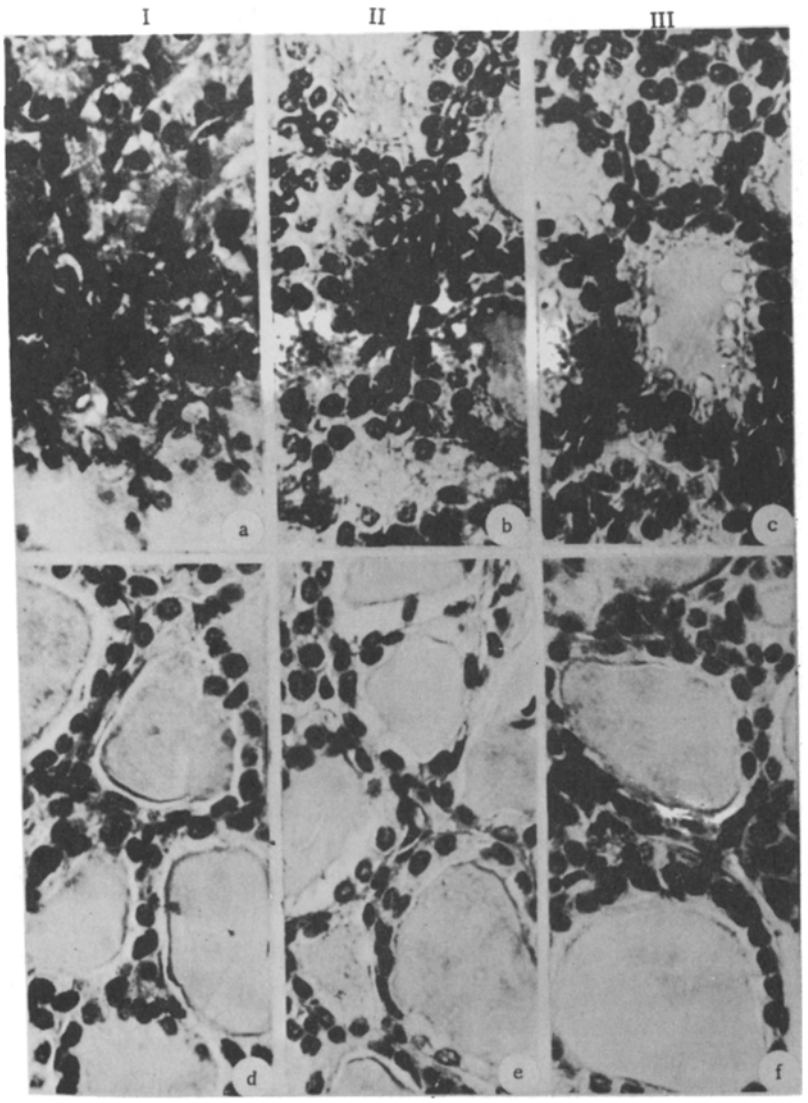
METHODS AND MATERIALS

Ninety-two young mongrel dogs aged $1\frac{1}{2}$ to 5 months, and 126 white rats weighing 120-160 g were selected.* All experiments were carried out according to the same plan. One lobe of the thyroid gland (the right) was entirely removed (average weight in rats about 7.63 mg). At the same time the caudal portion of the left lobe was resected in one of three ways: (1) 15-20% of the left lobe tissue was removed (Group I); (2) half of the left lobe was removed (Group II); and (3) 80-85% of the left lobe was removed (Group III).

In separate experiments, half of the animals remained without any kind of treatment while the other half received thyroid daily in a dose of 3 mg of thyroid per 100 g body weight. In additional experiments the thyroid dosage ranged from 1-5 mg. Powdered thyroidin, emulsified in water, was introduced directly into the stomach of the rats through a hollow rubber tube and was given to the dogs with a piece of food. Thyroidin supplementation began 3 days prior to operation and was continued throughout the period of observation.

The duration of the experiments with dogs was 12, 17, and 20 days and with rats, 10-20 days; in certain instances observation was continued over a month's time. It was not necessary to prolong the experiments further, for with time, a certain decline in hypertrophy occurs and regeneration progresses. Weighing of the remaining fragment of the left lobe of the thyroid and comparison of its weight with that of both lobes at operation was used to judge the degree of hypertrophy in the fragment remaining in situ. Apropos of the microstructure and functional state of the thyroid, changes in the height of the epithelium and the internal diameter of the follicles were assessed in histological preparations (fixed in Zenker's, Bouin's or Carnoy's solutions, stained with hematoxylin and eosin and with Schiff's Reagent for polysaccharide).

* Some of the experiments on dogs were described earlier [3].



The structure of the remaining fragment of thyroid in rats 20 days after operation. a, b, c) without thyroid replacement; d, e, f) with thyroid replacement. I) Minimal fragment preserved; II) half a lobe; III) maximum fragment. Microphotograph. Hematoxylin and eosin stain. Magnification 600×.

RESULTS

Comparison of data obtained in different experiments carried out at different times yields rather similar results.* Where a minimal fragment of thyroid tissue had been preserved, its weight within a short time had increased several times. The microscopic picture is characterized by extremely marked hyperplasia (with decrease in the PAS-reaction of the colloid and basal membrane of the follicles) which indicates the physiologic overexertion and functional exhaustion of the thyroid tissue (see table).

We have shown earlier that under conditions of biologic testing of markedly hyperplastic thyroid tissue in larval amphibians, it appeared entirely inactive (see photograph, a). This was the result of introduction of hormone in the organism [1, 10]. When half a lobe was preserved, hypertrophy was noted but was less prominent than in the previous

* Some experimental results have been presented at the Third All-Union Conference on the Problems of Regeneration and Cellular Reproduction, Moscow.

case; the number of mitoses in the cells lining the follicles was increased. Hypertrophy was less marked when a significant portion of the gland was preserved (see table). No signs of increased function were detected in the microstructure, as preservation of part of a lobe ensured sufficient hormone concentration (see photograph, b and c).

Mean Weight and Microstructure of Thyroid Fragments in Rats 20 Days After Operation

Condition of Expt.	Group	Inc. in wt. of fragment (%)	Ht. of epithelium (microns)		Follicle diameter (microns)	
			near injured area	other areas	near injured area	other areas
Without thyroid replacement	1	507	12,63	12,88	8,5	8,2
	2	72	10,05	8,46	19,6	24,0
	3	38	9,22	6,63	26,0	28,5
With thyroid replacement	1	12	4 7	3,6	32,4	35,0
	2	17	3,8	3,6	32,9	39,2
	3	8	4,2	3,4	30,7	37,6
Original state			7,28	5,36	26,8	30,4

Regeneration appeared in inverse ratio with hypertrophy. With a minimal tissue fragment remaining and marked compensatory hypertrophy, new follicles were not formed. In the second type of experiment, in which a larger fragment of thyroid was preserved, the hypertrophy was less marked and new follicles were formed in damaged areas. We had noted earlier in the studies on regeneration of thyroid tissue that formation of typical glandular structures was accompanied by activity in cells of mesenchymal nature which function to provide proper nutrition to the new follicles [3, 10]. The development of new tissue in a damaged region may have a multicentric nature which is determined by the type of vascularization and activity of the connective tissue elements involved in the stream of migration of epithelial cells. Regeneration was more marked when the ablation of a very small fragment of tissue did not entail hypertrophy in the remaining portion (see table).

We selected a dosage of thyroid so as to ensure the organism sufficient hormone to preserve functional activity after partial resection of a minimal fragment of the gland without increasing gland function (see photograph, d, e, f). Hyperemia was noted in parts of the thyroid near damaged regions. Hyperplasia and hypertrophy in the remaining portion of the gland was not observed in any of the three experimental variants throughout the entire observation period. Consequently, the increase in the preserved portion of the gland and the so-called compensatory reaction by no means follows injury but arises only in such instances in which there is a hormonal deficit in the organism. The formation of new areas of thyroid tissue is observed in roughly equal degree in all three experimental variants, i.e., is independent of the size of the fragment remaining.

Under conditions of thyroidization, significant activation of mesenchymal elements undoubtedly occurs and many small follicles form and grow, accumulating colloid. In different parts of the gland a decrease in follicular function is observed, which may be assessed by condensation of the thyroid epithelium and increase in homogeneous colloid (see table). Thus, artificial thyroidization, in the first place, prevents hypertrophy in the remaining fragment of the gland however small it may be, and, secondly, favors regeneration. It is probable that with more careful selection of thyroid dosages the degree of hypertrophy in the gland and the formation of new glandular structures in damaged areas might be regulated.

We see that so-called compensatory hypertrophy is by no means a reparative reaction of the organ to injury, but reflects only the level of functional strain in conditions of hormone deficit. Consequently, the reaction of an endocrine organ to partial resection is dependent equally on three factors: the effectiveness of the hormone, the functional potential of its secretory cells and the stimulating influence of the anterior pituitary. This last factor must be particularly considered in explaining the differences in reaction of thyroid tissue. In particular, we may—as the experiments in puppies showed—decrease hypertrophy in the remaining fragment of the thyroid gland by influencing the hypophysis without compensation by means of hormone replacement. This was ascertained by means of partial adrenalectomy performed at the time as the partial thyroidectomy. With simultaneous removal of one adrenal and half or three-quarters of the other, the thyroid gland fragment in situ did not enlarge or enlarged only very slightly,

showing the weakening of thyrotropic activity of the anterior pituitary. The reparative reaction in damaged areas was not lost; proliferation of glandular cells weakly forming follicles was noted.

The length of observation after the operation played an important role in revealing the relationship between regeneration and hypertrophy. In this connection, we focused on the extensive material we have gathered over a number of years during observations of various species of birds which have been subjected to subtotal thyroidectomy. In such observations we often conserve a small fragment of thyroid tissue [1]. Extremely small pieces of glandular tissue within a short time undergo marked hypertrophy. Initially they are not in a condition to compensate for the significant hormone deficit evoked by the operation, which is confirmed by the lack of ability of the feather follicles to develop new feathers in the trunk and neck. Longer observation showed that, with time, in certain birds the primary follicles reestablish their ability to develop. On dissection of such birds one always discovers a significant amount of glandular tissue in the operative region, having a typical microstructure but bearing signs of increased function. With a much longer period of observation (4, 6, or 8 months) not only does the regenerated size approach normal but the condition of the follicles, filled with homogeneous colloid, does not deviate from normal.

Thus, hypertrophy in an endocrine organ, occurring after its partial resection, is a physiologic reaction to a deficit of hormone. In this connection, it by no means can be considered as one of the means of self-restoration and, in particular, as one of the paths to reparative regeneration.

SUMMARY

Thyroid gland of young albino rats and puppies reacted by hypertrophy in response to hormone deficiency in the organism. Hypertrophy of the fragment left after partial resection is directly related to the size of the excized portion of the gland and does not favor the regeneration of a new thyroid tissue. Thyroidin administration prevents hypertrophy and stimulates the restorative processes in the thyroid gland.

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