REGENERATION OF THE THYROID GLAND

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The regeneration of the thyroid gland after its partial removal has been the subject of considerable research [1,2,4-7], and the ability of the gland to regenerate has been demonstrated. Meanwhile, the question of the extent to which regeneration of the thyroid can take place has been inadequately studied, and there is an almost complete absence of numerical data to qualify the process of regeneration. The mode of regeneration of the thyroid is particularly unclear. A. A. Voitkevich [1,2] considers that after resection, the missing part of the gland is restored by an outgrowth from the wound surface. This is unlikely, because most internal organs in mammals have not the power to regenerate in this way, but do so by what is called regeneration hypertrophy [3].

We have studied the method of regeneration of the thyroid gland and have obtained quantitative data concerning the changes taking place in the gland during regeneration.

EXPERIMENTAL METHOD

Experiments were conducted on 50 male albino rats weighing 220 g. The animals were kept on a standard pellet diet. Under ether anesthesia the whole of the right lobe and the posterior half of the left lobe, together with the isthmus of the thyroid, were removed, and the resected part was weighed on a torsion balance. No iodine was given during the operation. The rats were sacrificed 4, 8, 16, 31, and 93 days after the operation, and the residual part of the thyroid was extracted, weighed, and fixed in Bouin's fluid. Serial sections were cut to a thickness of 6-7μ, and stained by Heidenhain's azan method and with hematoxylin-eosin. Control animals were subjected to the trauma of the operation only; the thyroid was exposed and the wound closed. The relative proportions of epithelium, colloid, and stroma were determined by the methods of Uotila [8] and Tala [9]; the diameter of the follicles situated on a line passing through the pole of the gland was measured, their area was calculated, and the proportion of microfollicles to the total number of follicles was determined. By microfollicles we mean follicles less than 1000 μ^2 in area. The area of the follicles was determined from the formula for the area of a rectangle.

EXPERIMENTAL RESULTS

It will be seen from Table 1 that 8 days after the operation the residue of the thyroid gland enlarged until its weight was equal to that of one lobe of the intact gland. Between the 8th and 31st days after operation, the weight of the regenerating thyroid increased only very slightly. Three months later the weight of the thyroid was almost completely restored. The difference between the weights of the gland in the experimental and control animals was not significant ($P = 0.8$).

Four days after operation a typical picture of inflammation was observed on the wound surface, with infiltration of the tissues by leukocytes. Groups of epithelial cells were seen which were evidently the remains of destroyed follicles (Fig. 1). Some of these cells died, for their nuclei could be seen to be disintegrating. Mitotic figures were observed in some of the epithelial cells that were preserved. It is evident that these cells could eventually form new follicles. Meanwhile, numerous mitoses were seen in the follicles situated at some distance from the wound surface. A few isolated follicles were preserved in the region of the wound surface, and some of them were in the process of dividing into two new follicles by the formation of a central constriction (Fig. 2). It thus appeared that only those follicles injured at operation were destroyed, and that no dedifferentiation and destruction of the intact follicles took place.

Eight days after operation, the healing processes in the vicinity of the wound were complete and a firm scar had formed. Individual epithelial cells were rarely seen on the wound surface. Evidently the intact follicle cells, some of which were in process of multiplication, were taking part in the formation of new follicles.

TABLE 1. Weight of the Thyroid in Control and Experimental Rats

Time after operation (days)	Weight of gland (mg)		Ratio between weight of gland in experimental and control animals (in %)
	control	exptl.	
8	22.8	12.5	54.8
16	21.8	12.3	56.4
31	22.5	14.5	64.4
93	25.1	23.4	93.2

TABLE 2. Relative Proportions of Epithelium and Colloid in the Thyroid Gland of Control and Experimental Rats

Time after operation (days)	Epithelium (%)		Colloid (%)	
	control	exptl.	control	exptl.
8	61.6	72.2	28.5	19.1
16	53.8	79.4	38.6	14.0
31	54.1	76.4	38.9	16.5
93	54.6	60.9	39.3	33.3

TABLE 3. Number of Microfollicles as a Percentage of the Total Number of Follicles in the Thyroid of Control and Experimental Rats

Time after operation (days)	Control	Experimental
8	13.2	19.4
16	6.1	31.9
31	4.4	41.1
93	4.4	13.3

However, the changes we have described were not the only processes of regeneration. At this time the whole of the residual gland was engaged in regeneration. The marked hypertrophy of the follicular epithelium, which had become very high, was very noticeable. The lumen of most of the follicles had become reduced to a slit, and colloid was almost absent. In the remaining follicles the colloid had become liquid and stained blue with azan. Many mitoses were present throughout the regenerating gland (Fig. 3). In some areas there were masses of interfollicular tissue. The walls of the large follicles had become folded, and the folds extended deep into the lumen of the follicles. In some follicles the edges of the folds were in contact, as a result of which independent follicles were formed, containing the colloid from the maternal follicle. New microfollicles were also formed from the interfollicular tissue. These microfollicles could also be formed from the wall of a large follicle by budding. Eight days after operation no zonal changes could be observed.

Sixteen days after operation the same profound changes were seen in the residual gland as on the 8th day; the epithelium was high, the lumen of the follicles slitlike, and mitoses distributed throughout the gland and just as frequent as before. The formation of new follicles was also observed.

Thirty-one days after operation there were so many microfollicles that they dominated the picture. However, much interfollicular tissue was also observed. Mitoses were few, but binuclear cells were frequently seen. The wound surface was covered by a firm scar, in which were isolated follicles containing solid colloid.

Ninety-three days after operation the histological picture was very similar to that observed in the control animals. In the marginal areas of the thyroid there were large follicles with solid colloid. In some of these the epithelium was rather higher than normally. In the central zone medium-sized and small follicles were most numerous. Few microfollicles were present, but they were rather more numerous than in the control animals. No follicles with a slitlike lumen were present. The height of the epithelium was close to that in the control animals. A few mitoses were seen.

In one of the seven rats, after 93 days regeneration of the thyroid was slight. The weight of the gland amounted to 36.7% of the weight of the whole organ in the control animals. A firm scar was present on the wound surface, the follicular epithelium was strongly hypertrophied, the lumen of the follicles was slit-like, and much interfollicular tissue was present. The impression was created that the process of regeneration in this case was inhibited, and that the interfollicular tissue was unable to differentiate into new follicles.

It will be seen in Table 2 that the area occupied by the epithelium had increased 8 days after the operation by comparison with the controls, while the area occupied by colloid had diminished. After 93 days the relative proportion of epithelium and colloid had been restored to normal. The figures were slightly different from the control figures found at this time, but were very close to the indices observed in the control animals on the 8th day after operation.

Measurement of the area of the follicles enabled the number of microfollicles to be expressed as a percentage of the total number of measured follicles (Table 3).

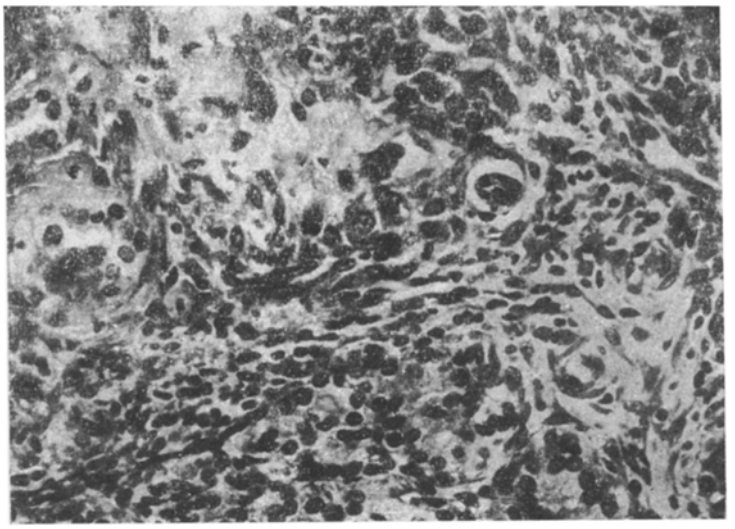

Fig. 1. Wound surface. Epithelial remnants of destroyed follicles (4 days after operation). Photomicrograph. Stained with hematoxylin-eosin. Magnification 280×.

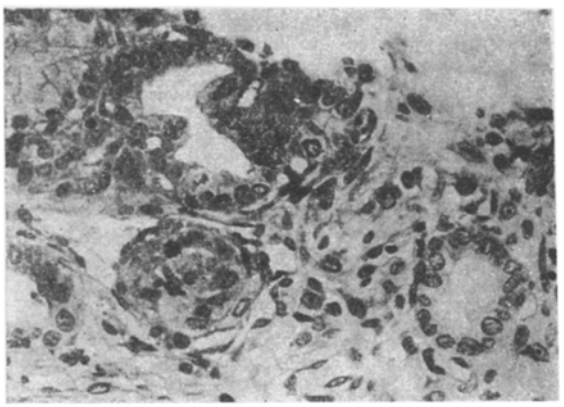

Fig. 2. Division of a follicle at the wound surface (4 days after operation). Photomicrograph. Stained with hematoxylin-eosin. Magnification 280×.

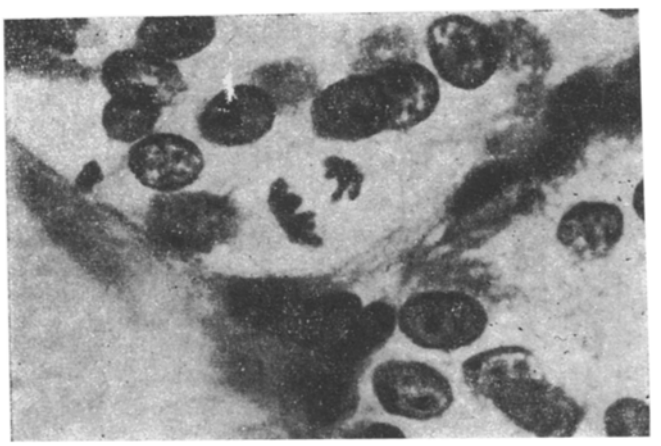

Fig. 3. Mitosis of the follicular epithelium at the anterior pole of the residue of the thyroid gland (16 days after operation). Photomicrograph. Stained with Heidenhain's azan. Magnification 1350×.

It will be clear from Table 3 that even at this early stage of regeneration new structural units were formed in the gland, i.e., new follicles. These new follicles were formed by the proliferation and differentiation of the interfollicular tissue, by budding of new follicles from existing ones, and also by the formation of several new follicles at the site of a preexisting large follicle as a result of the development of a central constriction or the budding of new follicles. The formation of new follicles progressed until the 31st day after operation.

Colloid subsequently accumulated in the microfollicles, because, on the 93rd day after operation the histological picture was very close to normal. A complete resemblance between the gland and its state in the controls could not, however, be observed at this time. As regards the number of microfollicles and the relative proportions of epithelium and colloid, the regenerating gland was very similar to the gland of the control animals 8 days after operation.

Hence, in the rat, in response to removal of the greater part of the parenchyma of the thyroid gland, a process of regeneration takes place, directed toward healing of the wound surface and increasing the mass of the functioning

tissue. The histological picture of the formation of new follicles at the wound surface indicates that the injured follicular epithelium is capable of proliferating. This process is ill defined and affects the zone immediately adjacent to the wound surface. However, these changes do not constitute the whole process of regeneration. Intensive mitotic division is observed in all parts of the regenerating thyroid gland, and mitoses are still frequent 16 days after operation, when the process of healing of the wound has long since been completed (see Fig. 3). Mitoses are found in the whole gland, including its anterior pole, i.e., the part of the gland furthest from the wound surface.

The process of formation of new follicles is progressive, and reaches its maximum on the 31st day. Hypertrophy of the follicular epithelium extends to all follicles, indicating the high functional strain. The state of hypertrophy is observed until the 31st day after operation. The processes of hypertrophy and proliferation of the follicular epithelium, and the formation of new follicles followed by the accumulation of colloid in them, ultimately lead to an increase in the mass of the organ, and 93 days after the operation its weight amounted to 93.2% of the weight of the gland in the control animals.

It may be concluded from the foregoing facts that regeneration of the thyroid gland is brought about mainly as a result of an increase in the mass of the residual gland and not as a result of the formation of new follicles at the wound surface. Consequently, the thyroid gland, like most other mammalian internal organs, regenerates principally not by the outgrowth of tissue from the wound surface, but as a result of an increase in the size of the whole residual organ, i.e., by regeneration hypertrophy.

SUMMARY

The right lobe and the posterior portion of the left lobe of the thyroid gland were excised in male albino rats weighing 220 mg. Postoperative observations periods were 4, 8, 16, 31, and 93 days. At the end of the experiment the weight of the regenerated gland was 93.2% of that in control animals. During the regeneration process mitosis of the follicular epithelium and formation of new follicules were observed in the thyroid remnant. The percentage ratio of the epithelium and the colloid, determined by Tal's method, at first showed a marked rise at the expense of the epithelium, later approaching the indices, characteristics of control animals. The percentage of microfollicules also showed a considerable increase (their percentage in 31 days reached 40). Later it dropped to normal values. Glandular regeneration took place not by growing from the wound surface, but by regenerative hypertrophy.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
