COMPENSATORY HYPERTROPHY OF THE RAT THYROID AFTER PARTIAL THYROIDECTOMY.

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Received for publication September 7, 1955.

REMOVAL of a large portion of the thyroid gland is followed by compensatory hypertrophy of the remnant. This observation, first recorded by Wagner (1884) has been confirmed many times and the literature reviewed by Loeb (1919), Marine (1926) and Cameron (1952). The experiments reviewed have not included any precise functional studies, and we have therefore measured the uptake of radioactive iodine (^{131}I) by the residual thyroid at varying time intervals after partial thyroidectomy. The findings were compared with the ^{131}I uptake of the thyroids of sham-operated controls and correlated with gland weight, histology and follicular cell height. We have tried to analyse the mechanism whereby function is restored to determine the time interval taken by the remnant to reach a steady state and to assess the rôle of the pituitary in this process.

MATERIALS AND METHODS.

Rats.—Stock albinos of mixed origin, mostly males of 250–350 g.

Operations.—All were done under ether anaesthesia. Hemithyroidectomy: the left lobe and left half of the isthmus were removed. Three-quarter thyroidectomy: the left lobe, isthmus and lower half of the right lobe were removed. Sham operations: the thyroid gland was exposed under anaesthesia, but not otherwise manipulated, in all of the controls. Hypophysectomy: the basi-sphenoid was exposed through the lateral pharyngeal approach, drilled and the pituitary sucked out. Completeness of the operation was confirmed at necropsy by examination of the pituitary fossa through a lens and by the finding of gross atrophy of the adrenals and gonads. Adrenalectomy: the left adrenal gland was removed through an incision in the back. There was a post-operative mortality and in addition all rats which did not appear to have made a good recovery from the partial thyroidectomy or hypophysectomy were killed. This led to the loss of 20 animals. The survivors only are enumerated in the experiments below.

Techniques.—After killing the rats with coal gas, the thyroids were removed attached to the trachea, fixed 4 hr. in Helly's fluid and washed overnight in running tap water.

Measurement of radioactivity.—After fixation and washing, each thyroid still attached to trachea was suspended at a fixed point in a standard $1\frac{1}{2} \times \frac{3}{4}$ in. (3·6 × 1·8 cm.) screw-capped vial and counted in the multitube Geiger-Müller ring counter described by Veall and Baptista (1954). The count rates given by these thyroids represented organically bound ^{131}I only, since most inorganic iodide had been washed out of the tissues. We confirmed this in a preliminary trial with 6 rats in which organic binding had been prevented with propylthiouracil. Following an injection of ^{131}I most of the radioactivity was found in the fixing and washing fluids. We also confirmed the validity of our method of measuring radioactivity in 6 rats 3 days after injection of ^{131}I, by which time practically all the ^{131}I in the thyroid is organically bound. The fixing and washing fluids were virtually free of ^{131}I, the count rates of the solid

glands corresponded excellently with subsequent measurement of fluid digests of the same thyroid glands.

In vivo counting of thyroid radioactivity was carried out by immobilisation of the rats under ether anaesthesia in the holder and multitube ring counter described by Arnott and Fossey (1952).

Weighing.—After measurement of radioactivity each thyroid was dissected off the trachea, freed of muscle, and weighed to the nearest 0·2 mg. on a torsion balance.

Histological methods.—After weighing, the thyroids were dehydrated in alcohol, cleared in chloroform and embedded in wax so as to be cut horizontally through the level of the isthmus. Sections were cut at 5 μ and stained by haematoxylin and eosin and by the periodic acid Schiff (P.A.S.) method.

Measurement of cell heights.—Done at oil immersion magnification on the P.A.S.-stained sections with a calibrated linear micrometer eyepiece. The eyepiece was swivelled round and every follicle cell measured whose long diameter lay directly over the image of the linear micrometer. The microscope stage was moved field by field so as to cover the sections completely both longitudinally and transversely : 100 cells were measured in each gland.

Hormone preparations.—L-Thyroxine (Glaxo) was freshly prepared as follows : 5 mg. crystalline L-thyroxine was dissolved in 1·0 ml. 0·1 N-NaOH and the solution diluted in 50 ml. saline. ACTH : Armour's acthar gel, 10 Armour units per ml. T.S.H. : Armour's thytropar, freshly dissolved in saline before use.

EXPERIMENTAL.

Changes in Residual Thyroid Tissue at Varying Time Intervals after Partial Thyroidectomy.

In order to measure the response of the thyroid to hemithyroidectomy 7 groups of rats, an average of 20 per group, were treated as follows. The rats in each group were operated upon on the same day, alternate animals being hemithyroidectomised and sham-thyroidectomised, and were kept in the same cage. They were of similar weight. At 7 different time intervals varying from 2 hr. to 120 days after the operation groups of rats were injected intraperitoneally with 15 μC ^{131}I and killed 2 or 3 hr. later. The thyroid or thyroid remnant was removed, fixed, weighed, its radioactivity measured ; the gland was sectioned and the average follicle cell height determined. Additional three-quarter-thyroidectomised rats were added to the 55- and 120-day groups. We chose a small time interval after ^{131}I injection for the measurement of iodine uptake by the thyroid because we thought there would be no significant output of labelled hormone in under 3 hr., even under conditions of a marked increase in thyroid activity.

The *results* are summarised in Table I and the Figure. The mean weight at 5 hr. of 55 per cent and ^{131}I uptake of 61·6 per cent of the controls represented the tendency in our rats of the right lobe to be slightly larger than the left. The residual lobe after hemithyroidectomy did not increase in weight during the 10 days following the operation. The findings at 25, 55 and 120 days of 63, 71 and 64 per cent as compared with 55 per cent at 5 hr. are suggestive, but by no means definite, of a slight weight gain. By 3 days ^{131}I uptake had risen to 86 and at 10 days to 91 per cent and thereafter did not show any statistically significant difference from the uptake of the controls. By 3 days there was a significant increase in mean follicle cell height of the residual lobes to 118 per cent of the controls. The mean cell height increased further to 131 per cent at 6 and 140 per cent at 10 days. Thereafter the cell height showed no further increase but varied from 137 per cent at 25 to 127 per cent at 130 days. The

residual half lobes of the three-quarter-thyroidectomised rats appear to have reached a fairly steady state by 4 months. They weighed 37 per cent of the controls at both 55 and 120 days : the ^{131}I uptake was within normal limits and the mean follicle cell height was 158 and 133 per cent. There was no significant difference in body weight between the controls and partially thyroidectomised rats within any one group. They all gained weight normally. Thus, for example, in the 55-day group the controls weighed 250 $\pm$ 19 g. at the beginning of the experiment and 336 $\pm$ 22 g. when killed ; the hemithyroidectomised 253 $\pm$ 19 g.

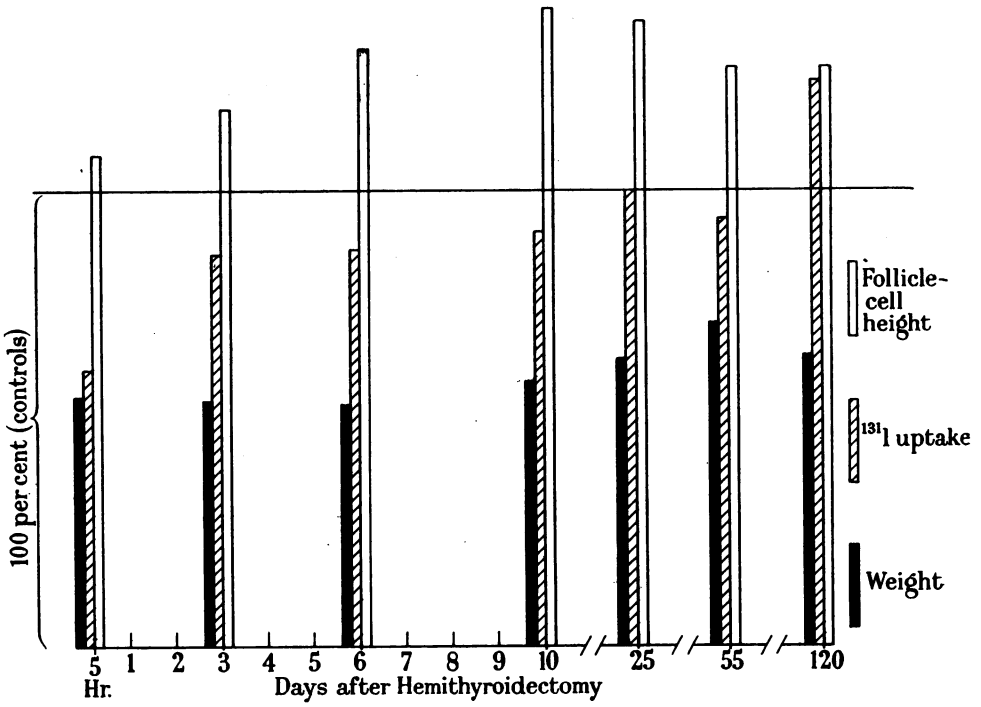

FIGURE.—Weight, ^{131}I uptake and follicle cell height of residual lobe of thyroid after hemithyroidectomy expressed as a percentage of the controls' intact thyroid weight, ^{131}I uptake and follicle cell height.

and 351 $\pm$ 35 g. respectively ; and the three-quarter-thyroidectomised 257 $\pm$ 26 g. and 340 $\pm$ 36 g.

Microscopy showed follicle cell hypertrophy in the residual lobes from the 3rd day onwards. The cytoplasm was more voluminous and less densely eosinophilic and the cells showed an obvious increase in height. A very occasional follicle cell mitosis was observed in the residual lobes on the 3rd, 10th, 25th, 55th and 120th days. The colloid appeared less in quantity, less densely eosinophilic and more vacuolated than that of the controls. The interfollicular capillaries were larger and produced a marked indentation of the follicular cells. These changes were all more advanced in the centrilobular than in the peripheral follicles. There was no apparent increase in the number or size of follicles, although the lobules appeared more loosely packed.

TABLE I.—*Changes in Thyroid Weight, Follicle Cell Height and ^{131}I Uptake at Varying Time Intervals after Partial Thyroidectomy.*

Time interval after partial thyroidectomy.	Group.	Number of rats.	Mean thyroid weight (mg.) + S.D. of mean.	Residual thyroid lobe weight as per cent of controls.	Mean thyroid uptake of ^{131}I in 1000 counts/min. + S.D. of mean.	Residual lobe ^{131}I uptake as per cent of controls.	Mean thyroid follicle cell height (μ) + S.D. of mean.	Residual thyroid lobe follicle cell height as per cent of controls.
5 hours	Controls	10	21·7±2·4		10·6±2·9		6·93±2·41	
	Hemithyroidectomy	10	11·9±1·5	55	6·4±1·5	61	7·49±0·72	108
3 days	Controls	11	30·3±3·9		3·7±0·9		7·34±0·61	
	Hemithyroidectomy	10	16·2±2·0	54	3·2±0·7	86	8·66±0·35	118
6 ,,	Controls	10	23·6±3·1		1·7±0·5		6·88±0·58	
	Hemithyroidectomy	10	12·4±2·1	53	1·5±0·4	87	9·01±1·27	131
10 ,,	Controls	10	24·6±4·3		3·2±1·6		5·93±0·61	
	Hemithyroidectomy	11	14·3±2·3	58	2·9±1·0	91	8·32±0·94	140
25 ,,	Controls	10	27·8±3·8		3·0±0·7		7·07±0·66	
	Hemithyroidectomy	10	17·6±3·0	63	3·0±0·7	100	9·69±0·70	137
55 ,,	Controls	8	26·3±4·7		1·6±0·5		8·30±1·46	
	Hemithyroidectomy	8	18·7±3·7	71	1·5±0·5	94	10·20±1·99	127
	Three-quarter thyroidectomy	8	9·8±3·1	37	1·5±0·5	94	13·15±1·64	158
120 ,,	Controls	9	32·3±3·0		1·6±1·0		7·46±0·82	
	Hemithyroidectomy	9	20·7±3·6	64	2·0±0·9	124	9·45±0·74	127
	Three-quarter thyroidectomy	8	11·9±3·6	37	1·5±0·8	94	9·91±0·72	133

The rats were each injected with 15 μc ^{131}I 2 or 3 hr. before they were killed The radioactivity of the thyroids of any one group was assayed at the same time. The variation in count-rate between groups is due mainly to variation in the time interval of assay after removal of the thyroids.

Rate of Loss of ^{131}I from the Thyroid after Three-quarter Thyroidectomy.

The finding of a maintained increase in follicle cell height in the residual lobe is evidence of an increased stimulation by pituitary thyrotrophic hormone (T.S.H.). We tried to find an objective measure of the associated colloid store. The smaller colloid store in the partially thyroidectomised rats is likely to be associated with a smaller store of thyroid hormone. This would result in a higher ratio of labelled to unlabelled hormone in a tracer experiment. The higher specific radioactivity of the stored hormone would lead to a more rapid loss of ^{131}I from the residual lobe though the total output of hormone, labelled + unlabelled, would be the same as that of the control thyroids. The rate of loss of ^{131}I from the thyroid was measured in the following experiment.

Ten rats three-quarter-thyroidectomised 2 months previously and 11 sham-thyroidectomised rats were injected intraperitoneally with 25 μc ^{131}I. Their thyroid radioactivity was measured *in vivo* under ether anaesthesia at intervals of 12, 24, 36, 60, 84, 102 and 132 hr. after the injection. At each interval the counts/min. registered were recorded as a percentage of the standard dose of 25 μc ^{131}I counted at the same time. The results, plotted on semi-logarithmic paper, showed a steady fall in thyroid radioactivity from 36 hr. onwards (radioactivity ordinate and hours abscissa). The *slope* of this line was measured for each individual rat (fall in height per unit length of abscissa).

Results.—The percentage uptake of ^{131}I into the thyroid varied considerably between the rats. The average was 22·6 per cent (18·3–27·5) at 12 hr. in the controls, was about the same at 24 hr., dropped to 20·1 per cent at 36 hr. and fell steadily to 12·1 per cent (9·6–15·5) at 132 hr. The three-quarter-thyroidectomised groups showed a lower average content of ^{131}I at 12 hr., *i.e.*, 17·4 per cent (13–22·5) which dropped to 15·4 per cent at 36 hr. and then also fell steadily to 7·1 per cent (3·8–10) at 132 hr. The loss of ^{131}I from the thyroid was significantly greater in the three-quarter-thyroidectomised animals. The mean thyroid ^{131}I was 46 per cent of the 36 hr. content at 132 hr. in the three-quarter-thyroidectomised rats and 60 per cent in the controls. This was confirmed by the mean slope of the plotted points : 0·209 against 0·1376. Student's t-test gave a significance of $P < 0{\cdot}001$ for both methods of recording the difference in fall of radioactivity. The difference is reduced by the further uptake into the thyroid of ^{131}I released from the metabolism of labelled hormone in the periphery. Owing to the higher specific radioactivity of the thyroid hormone in the partially thyroidectomised rats, more ^{131}I is made available for re-use than in the controls.

Effect of Thyroxine and of Hypophysectomy on Compensatory Hypertrophy of the Thyroid.

Since pituitary T.S.H. is known to increase thyroid follicle cell height and reduce the colloid store, the results (Table I) suggest dependence of the compensatory hypertrophy response on an intact hypothalamic pituitary mechanism. This mechanism is likely to be stimulated to an increased output of T.S.H. following the temporary drop in thyroxine secretion from the hemithyroidectomised thyroid. Though this seems obvious it is nevertheless also possible that some degree of thyroid hypertrophy might be independent of the pituitary.

We therefore designed the following experiment to see if hypophysectomised rats show any degree of compensatory reaction after hemithyroidectomy. We added a group of non-hypophysectomised animals in which T.S.H. output was inhibited by the daily administration of a large dose of thyroxine.

The animals were arranged in four groups. The 22 rats in the first group were injected daily with 16 μg. L-thyroxine subcutaneously. After 3 days 11 of them were hemithyroidectomised and 11 sham-hemithyroidectomised. The thyroxine injections were continued and 24 hr. later they were all given an intraperitoneal injection of 50 μc ^{131}I and killed after 18 hr. The thyroids were fixed, their radioactivity measured, and they were weighed and sectioned. The remaining groups, 15, 18 and 12 rats respectively were all hypophysectomised and half of them hemithyroidectomised and half sham-hemithyroidectomised. In the last group the thyroid operation was done 21 days after the hypophysectomy. Two groups were killed 27 days and one 22 days after the hemithyroidectomy 18 hr. after receiving 50 μc ^{131}I. The thyroids were fixed, their radioactivity measured and they were weighed and sectioned. The interval of 18 hr. ^{131}I uptake rather than 3 hr. was chosen because of the extremely slow iodine uptake which follows hypophysectomy.

The *results* summarised in Table II show no evidence of any gain in weight of the residual lobe after 3 to 4 weeks. They averaged 42–54 per cent of the controls. Nor was there any evidence of any increased function. The mean ^{131}I uptake of the residual lobe compared with the control lobes was 60 per cent in the thyroxine-treated animals and varied from 52–28 per cent in the hypophysectomised groups. (The ^{131}I uptake showed a strikingly larger variation from rat to rat than that previously observed in the intact animals).

Microscopic examination showed no difference between the residual lobes and control thyroids in this experiment. The follicles rich in colloid, were all lined by a remarkably thin epithelium, barely 2 μ in height. Measurement of the height of these remarkably flattened cells was in effect measurement of nuclear thickness. Any difference between residual lobes and controls in this experiment was too small for us to detect. The picture was essentially the same in both the thyroxine-treated and the hypophysectomised groups.

Comparison of the Residual Thyroid and Adrenal after Hemithyroidectomy and Unilateral Adrenalectomy with Control Thyroid and Adrenals in Hypophysectomised Rats Treated with the Same Dose of T.S.H. and ACTH.

The findings in the previous experiment of no functional or morphological evidence of compensatory reaction after thyroidectomy in the absence of T.S.H. confirm the essential rôle of the pituitary in the process of compensatory hypertrophy of the thyroid. Since thyroid tissue is known to inactivate T.S.H. *in vitro* (Rawson, Sterne and Aub, 1942) it is conceivable that the freshly hemithyroidectomised rat might use up circulating T.S.H. at only half the rate of control rats. Thus, a "normal" output of T.S.H. from the pituitary might lead to an increased blood level in the hemithyroidectomised animal which would consequently lead to hypertrophy of the residual lobe. To investigate this possibility we compared the function and histology of the hemithyroidectomised thyroid with that of the whole gland in hypophysectomised rats given daily injections of the same quantity of exogenous T.S.H. Thus, if thyroid tissue *per se* plays a chief rôle in the removal or destruction of T.S.H., the animals

TABLE II.—*Effect of Thyroxine Treatment and of Hypophysectomy on Compensatory Hypertrophy of the Thyroid after Partial Thyroidectomy.*

Treatment.	Group.	Number and sex of rats.	Mean body weight (g.) + S.D. at time of hypophysectomy.	Mean body weight (g.) + S.D. at time of killing.	Mean thyroid weight (mg.) + S.D. of mean.	Residual thyroid lobe weight as per cent of controls.	Mean thyroid uptake of ^{131}I in 1000 counts/min. + S.D. of mean.	Residual thyroid lobe ^{131}I uptake as per cent of controls.
16 μg. L-thyroxine daily for 27 days. Hemithyroidectomy 3 days after commencement of treatment. Killed 24 days later	Thyroxine only	10 M.	—	313±38	22·7±4·3	—	0·89±0·20	—
	Thyroxine and hemithyroidectomy	11 M.	—	325±24	12·1±3·2	53	0·53±0·25	60
Hypophysectomy and hemithyroidectomy on same day. Killed 27 days later	Hypophysectomy only	9 M	283±12	214±10	17·0±2·5	—	2·49±0·84	—
	Hypophysectomy and hemithyroidectomy	6 M.	278±21	208±12	7·6±1·6	45	1·15±0·61	46
Hypophysectomy and hemithyroidectomy on same day. Killed 22 days later	Hypophysectomy only	8 M.	276±18	248±19	14·9±3·7	—	3·72±1·59	—
	Hypophysectomy and hemithyroidectomy	10 M.	278±25	237±21	6·3±1·3	42	1·94±1·32	52
Hypophysectomy followed 21 days later by hemithyroidectomy. Killed 27 days after hemithyroidectomy	Hypophysectomy only	6 F.	243±30	193±21	14·6±2·8	—	8·29±4·43	—
	Hypophysectomy and hemithyroidectomy	6 F.	239±14	193±30	7·9±2·1	54	2·33±1·75	28

The rats were each injected with 50 μc ^{131}I 18 hr. before they were killed.

with only one thyroid lobe should show a greater stimulation of the thyroid tissue than those with two lobes. We considered that the health of these hypophysectomised animals would benefit from the possession of adrenals which were functioning and therefore gave them ACTH in addition to T.S.H. We also extended the experiment by the removal of one adrenal in the hemithyroidectomised rats. This allowed us to study the quantitative response of the adrenal to its pituitary trophic hormone in the same way as the thyroid.

The thyroid and adrenals always atrophy after hypophysectomy. We therefore did a preliminary experiment on 6 hypophysectomised rats using two different doses of T.S.H. and ACTH to find how much hormone must be given daily to maintain a normal thyroid and adrenal weight. This was effected by 0·75 Armour units ACTH and 0·3 U.S.P. units T.S.H. per day. The main experiment was then carried out. Twenty-five rats were hypophysectomised and in 12 of them an additional hemithyroidectomy and removal of the left adrenal was performed. After 3 days and for the ensuing 10 days all the animals were given daily ACTH and T.S.H. All the animals were killed 24 hr. after the last dose of ACTH and T.S.H. : 3 hr. before death they were injected intraperitoneally with 30 μc ^{131}I. The thyroids and adrenals were fixed, weighed and sectioned. The bound ^{131}I content of the thyroids was measured.

The *results*, summarised in Table III, show clearly that the residual thyroid lobe and adrenal gland were not stimulated more than the control glands. The residual thyroid lobe weighed 56 per cent, gave a 59 per cent ^{131}I uptake, and showed a mean cell height of 102 per cent of the controls. The residual adrenal gland weighed 52 per cent of the controls. Thus there is no evidence that the blood levels of T.S.H. and ACTH were higher in the hemithyroidectomised and hemiadrenalectomised animals. The mean follicle cell height of 6 μ compared favourably with the 6–8 μ found in unhypophysectomised controls (Table I) and contrasted with the 2 μ found in the hypophysectomised rats not given T.S.H. (Table II).

DISCUSSION.

Our findings confirm those of previous workers that there is a compensatory hypertrophy of the residual lobe following hemithyroidectomy (Table I). We have shown that there is a restitution of function to normal (Table I), that this

TABLE III.—*Comparison of the Unilateral Thyroid and Adrenal after in Hypophysectomised Rats Treated with the*

Treatment.	Number of rats.	Mean body weight (g.) + S.D. at time of operation.	Mean body weight (g.) + S.D. when killed
Hypophysectomised and killed 14 days later. Given daily parenteral T.S.H. and ACTH from the 3rd to the 14th day.	13	295±21	258±13
Hypophysectomised hemithyroidectomised, hemiadrenalectomised and killed 14 days later. Given daily parenteral T.S.H. and ACTH from the 3rd to the 14th day.	12	296±13	252±18

The daily dosage of T.S.H. was 0·3 U.S.P. units and of ACTH was 0·75 Armour units per rat.

depends on secretion of T.S.H. by the pituitary (Table II) and that it is likely to be due to an increased pituitary output rather than a diminished destruction of T.S.H. (Table III). Following hemi- or three-quarter thyroidectomy the gland is restored to normal function by a maintained cell hypertrophy and associated decreased colloid store and hormone store (Table I). This state was seen as long as 4 months after hemithyroidectomy. Hypothetically, function might have been restored after hemithyroidectomy by a twofold increase in the number of cells. Restitution of the liver after two-thirds hepatectomy in the rat is brought about by an increase of the number of cells in the stump to the number in the whole control liver (Brues, Drury and Brues, 1936). However, we found no obvious increase in the number of follicles, diameter of follicles or number of nuclei per follicle in the residual thyroid lobes after partial thyroidectomy. Nevertheless, although we cannot rule out a slight degree of cell multiplication, we are confident on histological grounds that increase in cell height and not number is the characteristic pattern seen in compensatory hypertrophy after a hemi- or three-quarter thyroidectomy.

The finding of a maintained increase in follicle cell height is evidence of an increase in the level of circulating T.S.H. The thyroid gland is capable of hyperplasia to a ten- or twentyfold increase in its mass and cell number under the stimulus of excessive endogenous T.S.H. produced by dietary iodine deficiency or goitrogens. One must conclude that the rise in T.S.H. output following hemi- or three-quarter thyroidectomy is far below that following thiouracil administration. A relatively small number of hypertrophied cells is probably able to maintain an output of thyroid hormone sufficient to prevent the order of rise of T.S.H. output which obtains in goitrogen experiments. We picture the sequence of events as follows : Hemithyroidectomy is immediately followed by a moderate fall in level of circulating thyroid hormone. This leads to a moderate rise in T.S.H. output by the pituitary which produces a sufficient hypertrophy of the thyroid cells to bring the blood level of thyroxine up to normal. From then onwards there is no extra rise of thyroxine to diminish T.S.H. output nor any drop in thyroxine level to stimulate a further rise in T.S.H. output. Thus the animal is set with a smaller than normal thyroid made up of hypertrophied cells and diminished colloid associated with a raised level of T.S.H. The greater the initial fall in blood thyroxine level, *i.e.*, the greater the mass of thyroid tissue

Hemithyroidectomy and Hemiadrenalectomy with Control Intact Glands Same Dosage of T.S.H. and of ACTH.

Mean thyroid weight (mg.) + S.D. of mean.	Residual thyroid lobe weight as per cent of controls.	Mean thyroid per cent ^{131}I uptake + S.D. of injected ^{131}I.	Mean residual thyroid lobe ^{131}I uptake as per cent of controls.	Mean thyroid follicle cell height (μ) + S.D. of mean.	Mean residual thyroid lobe follicle cell height as per cent of controls.	Mean total adrenal weight (mg.) + S.D of mean.	Residual adrenal weight as per cent of controls.
19·3±3·0	—	3·2 ±0·84	—	6·04±0·71	—	27·9±3·3	—
10·8±2·1	56	1·89±0·66	59	6·17±0·42	102	14·4±1·7	52

The rats were each injected with 30 μc ^{131}I 3 hr. before they were killed.

initially removed, the higher will be the subsequent rise in T.S.H. Following removal of the majority of the gland one would expect a rise in T.S.H. sufficient to produce the formation of a marked increase in number of cells in addition to cell hypertrophy. Bielschowsky (1949) has shown that the goitrogen-induced excessive rise of T.S.H. which in combination with acetylaminofluorene (A.A.F.) produces thyroid tumours can also be induced by subtotal thyroidectomy. Tumours arose in the residual isthmus of rats treated with A.A.F. following operative removal of both lobes, without any thiouracil treatment.

In our experiments there was only a questionable increase in mass of the residual lobe. The residual lobe after hemithyroidectomy increased at the most by about 20 per cent and the residual half lobe after three-quarter thyroidectomy by about 15 per cent (Table I). Histological study suggested that part of this increase might be due to a greater capillary mass. Very occasional mitoses were seen which might represent some degree of hyperplasia. However, they may also indicate that hypertrophied cells are renewed at a greater rate than non-hypertrophied ones. The residual thyroid tissue can markedly increase its cytoplasmic mass with little change in total mass (Table I). This property is dependent on the lability of the colloid store which diminishes in volume *pari passu* with follicle cell hypertrophy. The intrafollicular spaces in goitrogen-treated rats become mere slits. This reserve of space is of cardinal importance in modifying the pattern of compensatory hypertrophy in the thyroid in contrast to the increase in total weight which occurs in the liver, adrenals and kidneys.

We have so far, in our discussion, neglected the possible rôle of anterior pituitary growth hormone, somatotrophin. It is certainly possible that compensatory hypertrophy of the thyroid is potentiated by somatotrophin. One might argue that failure of the thyroid remnant to hypertrophy in the hypophysectomised rats (Table II) was due to the lack of growth hormone rather than lack of T.S.H. However, in Group 1 (Table II) growth hormone was available but the secretion of T.S.H. was totally inhibited by daily thyroxine administration. Thus T.S.H. would appear to be the major stimulus to compensatory hypertrophy of the thyroid.

Our findings can be summed up by Cameron's (1952) definition that " hypertrophy is controlled growth governed by the need to be overcome ". In the rat thyroid, partial removal is followed by a rapid restitution of function effected chiefly by a maintained cell hypertrophy mediated through the pituitary secretion of T.S.H. The thyroid differs from the rat liver in which function is restored by eventual restoration of the cells in number rather than by a permanent increase in the cytoplasmic mass of each cell.

SUMMARY.

The average ^{131}I uptake, weight and follicle cell height of the residual thyroid lobe was compared with controls at varying time intervals after hemi- and three-quarter thyroidectomy in adult rats.

^{131}I uptake fell to about half after hemithyroidectomy but was restored to normal within 10 days. This was associated with follicle cell hypertrophy and diminished colloid storage which was maintained in a steady state for the 4 months studied.

The diminished colloid store was found to be associated with an increased rate of loss of ^{131}I from the residual lobe.

There was no functional increase or compensatory hypertrophy in the residual lobes of rats hypophysectomised or treated with L-thyroxine.

No compensatory hypertrophy of the thyroid and adrenal was found in hypophysectomised rats, half of them hemithyroidectomised and unilaterally adrenalectomised, all of them maintained by daily injections of a fixed dosage of exogenous T.S.H. and ACTH.

On these findings it was considered that after hemi- or three-quarter thyroidectomy in the rat compensatory hypertrophy of the residual lobe is effected by an increased output of endogenous T.S.H. at a level which gives rise to a degree of individual cell hypertrophy and associated diminished colloid storage sufficient to restore total thyroid function to normal. This state is maintained at least as long as 4 months. There is no restitution to a normal total number of follicle cells associated with a normal colloid store.

We are indebted to the Medical Research Council for a personal grant to one of us (J. H. L.).

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