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The Histological Effects of Tapazole on Rat Thyroids, Hearts, and Adrenals

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The Histological Effects of Tapazole on Rat Thyroids, Hearts, and Adrenals

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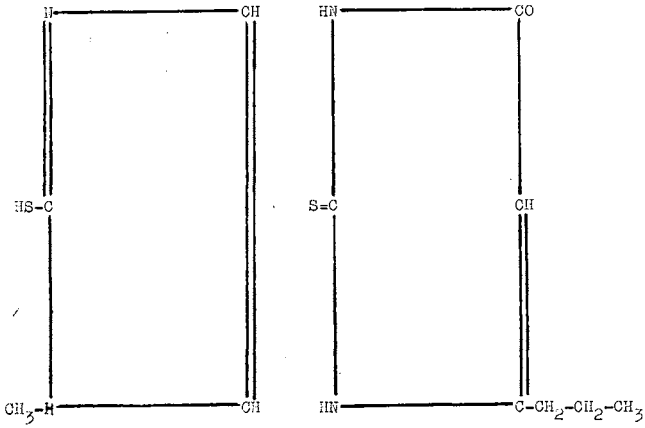
Abstract. The anti-thyroid drug Tapazole, when fed to white rats at the dietary level of 0.1% Tapazole in finely ground laboratory meal, produces changes in body weight, thyroid weight and in the histological composition of the thyroid. Histological examination shows that the affected thyroids have undergone hypertrophy and hyperplasia. Tapazole does not seem to affect rat hearts or adrenals.

The white crystalline, anti-thyroid drug, Tapazole,[2] 1-methyl-2-mercaptoimidazole, is the most powerful one known today, with amounts as small as 0.5 mg having a profound effect on the human thyroid gland. "Tapazole differs from drugs of the thiouracil series [such as Propylthiouracil] chiefly in having a five-membered instead of a six-membered ring," (Lilly, 1963).



Tapazole Propylthiouracil

Figure 1. Comparison of the structural formulae of the two goitrogenic drugs Tapazole and Propylthiouracil.

Since any organic change is related to individual cellular changes within it, one of the best ways to study any drug's effects is by means of histologic examination. Thus any effects Tapazole might have on the thyroid gland or any other organ

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[2] Tapazole, Methimazole, courtesy Dr. G. Irwin, Eli Lilly Co., Indianapolis, Indiana.

could first be observed on the cellular level. The purpose of this study was to observe what changes, if any, Tapazole has on the rat thyroid, heart and adrenals.

Methods

Nine six-week old female rats of the Holtzman strain were marked, weighed and placed in cages by pairs. One cage, however, held three animals. The animals were kept in a thermoregulated room maintained at 25 ± 2°C, which was illuminated for approximately nine hours per day. All animals were given tap water and Purina laboratory checkers for one week. After the week on standard diet, the animals were divided into two groups. The control group, four in number, continued to receive standard Purina laboratory checkers, while the experimental group, five in number, received a 0.1% mixture of Tapazole in finely ground Purina laboratory meal. Each animal was weighed weekly and the results tabulated. All animals appeared normal and responsive except one experimental that developed a 1-cm scar over the left shoulder. Since further examination determined a weight loss and a pronounced limp, this animal was isolated from the others and its records were not included in the study. After an eight-week period, all animals were sacrificed and weighed and the thyroids, hearts and adrenals removed. Organ weights were obtained by means of a Roller-Smith torsion balance and organ weights per 100 grams body weight ratios calculated.

Each individual organ was placed in a plastic bag containing an identifying number and buffered formalin. The organs were processed by a tissue processing machine, embedded, cut on a microtome at 5-6 microns, and divided into five sets of 27 slides each. One set was stained by the Hematoxyln and Eosin method; another by the Periodic Acid Schiff's reaction; and the third by the Goldner modification of the Masson Trichrome stain. The two remaining sets were not stained. Photomicrographs were taken of experimental and control thyroids and adrenals.

After a preliminary reading of each slide, a more comprehensive study was made of the thyroids. Four series of measurements of experimental and control tissue were made. These measurements were: (1) the average number of follicles per field; (2) the average diameter of the follicles; (3) the average number of epithelial cells per follicle; and (4) the average height of the follicular epithelial cells. In measurements 1 and 4, an ocular micrometer was used while the diameter of the high-power field was calculated at 350μ for measurement 1. Standard Deviation and Standard Error were calculated.

Results

Tapazole fed animals had a lower body weight than did the control animals, as shown in Fig. 2.

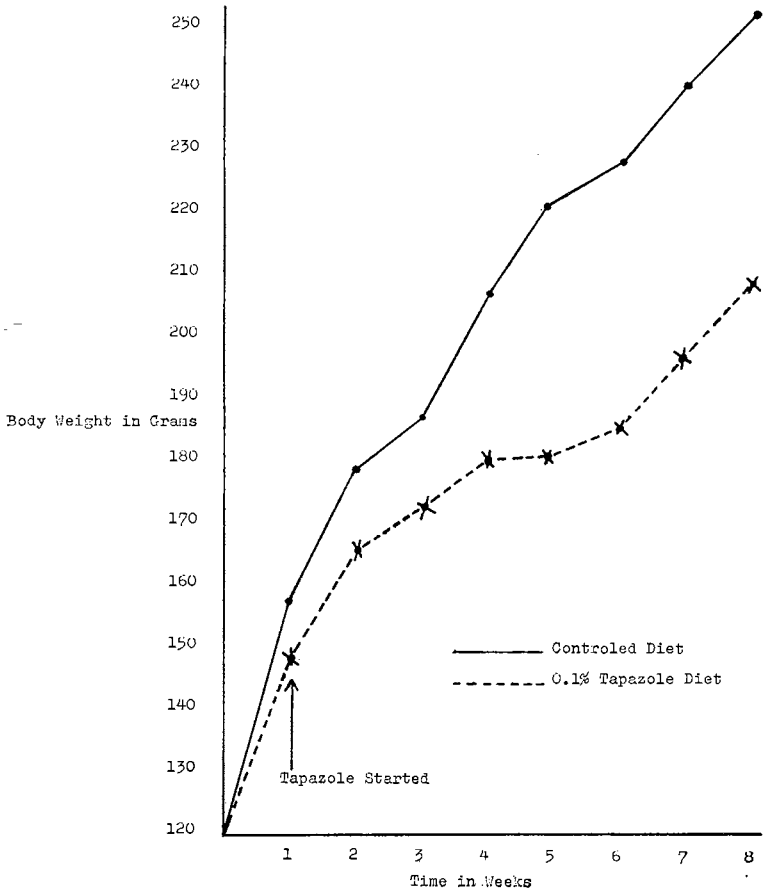

Figure 2. Effect of 0.1% Tapazole in diet on body weight.

Organ-weight to body-weight ratios are contained in Table 1. These show a considerable enlargement of the thyroid gland, a slight decrease in heart size and no significant change in the adrenals.

The most apparent histological change noted took place in the thyroids of the experimental animals. Low power microscopic examination of sections stained by the Hematoxylin and Eosin stain, Golder modification of the Masson Trichrome stain, and the Periodic Acid Schiff's reaction shows two differences. The thyroids of the experimental animals have approximately twice

Table 1. Body Weight and Organ Weight Per 100-Gram Body-Weight Ratios

Treatment		Body Weight	(mg/ 100 grams body weight)		
			Thyroid	Heart	Adrenals
Control	1	246.5	6.3	304.2	24.6
	2	245.5	6.1	333.0	17.2
	3	256.6	5.4	286.2	15.9
	4	256.6	6.2	317.5	22.1
(Average)		251.3	6.0	310.0	19.9
Tapazole	1	212.0	27.0	270.0	23.4
	2	217.6	18.8	236.0	22.0
	3	217.6	41.3	265.8	18.4
	4	189.0	24.6	252.2	25.8
(Average)		209.1	27.7	256.0	22.4

the number of follicles per field than the controls (see Table 2), and there is a sharp reduction in the amount of colloid present within the experimental sections.

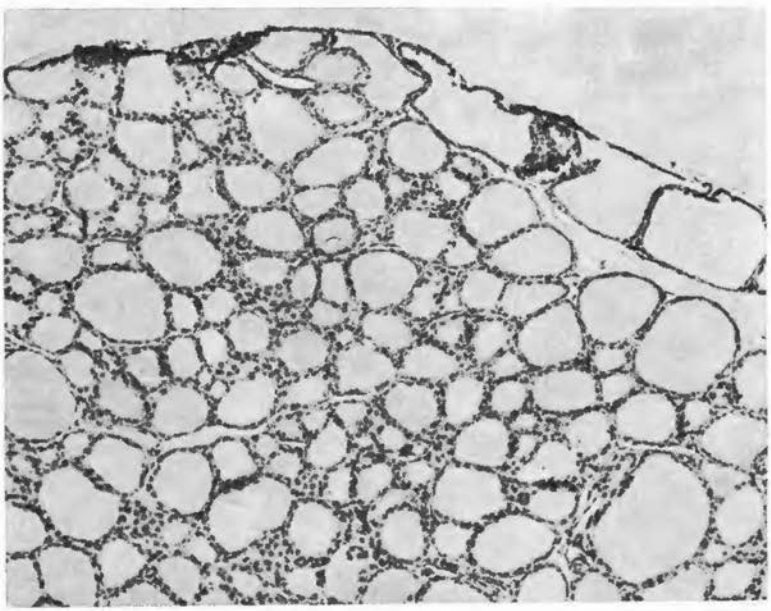

Figure 3. Low power photomicrograph of control thyroid. Compare with Figure 4. Hematoxylin and Eosin.

A high power examination of the two sets of slides shows that the follicular epithelial cells in the experimental animals are low columnar, whereas, the thyroids of the control animals show typical cuboidal epithelium. The average increase in height of the follicular cells of the experimental animals is approximately

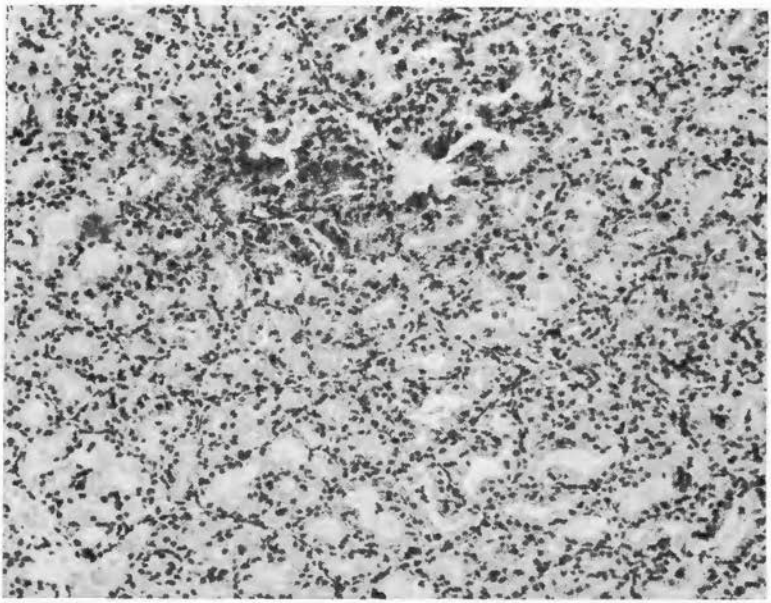

Figure 4. Low power photomicrograph of experimental thyroid. Hematoxylin and Eosin.

2.7 times (see Table 2). There is a slight decrease in the number of epithelial cells noted in the experimental sections, while the diameters of the experimental follicles average 30μ less than the controls.

Table 2. Comparison of Follicular Measurements

Average number of follicles per field. (Diameter of field = 350μ.)	
Controls	13.96 ± 0.3755
Experimentals	27.25 ± 0.1212
Average diameter of follicles.	
Controls	105.06 ± 3.452μ
Experimentals	74.64 ± 2.887μ
Average number of epithelial cells per follicle.	
Controls	24.10 ± 1.22
Experimentals	15.86 ± 0.7271
Average size of follicular epithelial cells.	
Controls	6.24 ± 0.238μ
Experimentals	17.13 ± 0.63μ

No histological changes were noted in the hearts or adrenals.

Conclusions

The anti-thyroid drug, Tapazole, effects changes in body weight, thyroid weight and the histology of the thyroid. Slight changes in heart size and adrenal size are not considered significant here.

A lower body weight in Tapazole-treated animals had been

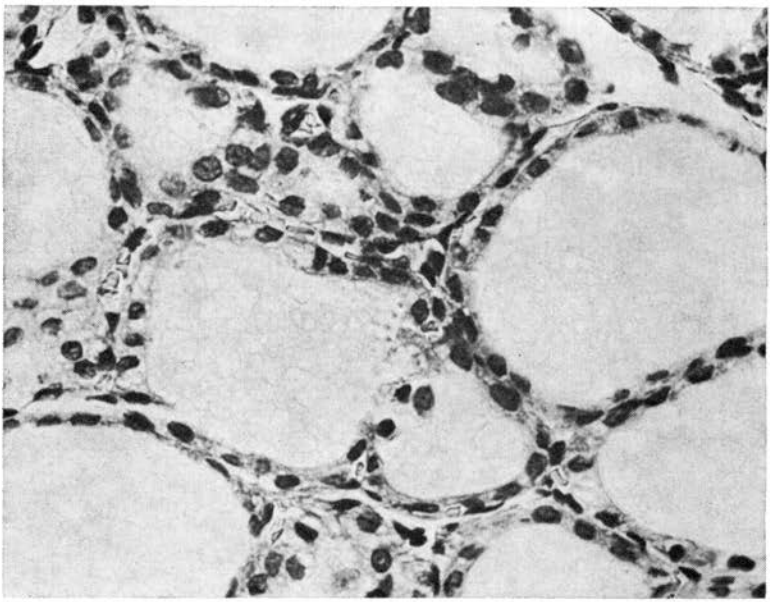

Figure 5. High power view of Figure 3. Compare follicular width, number of follicles in field, number and size of follicular epithelial cells with Figure 6. Hematoxylin and Eosin.

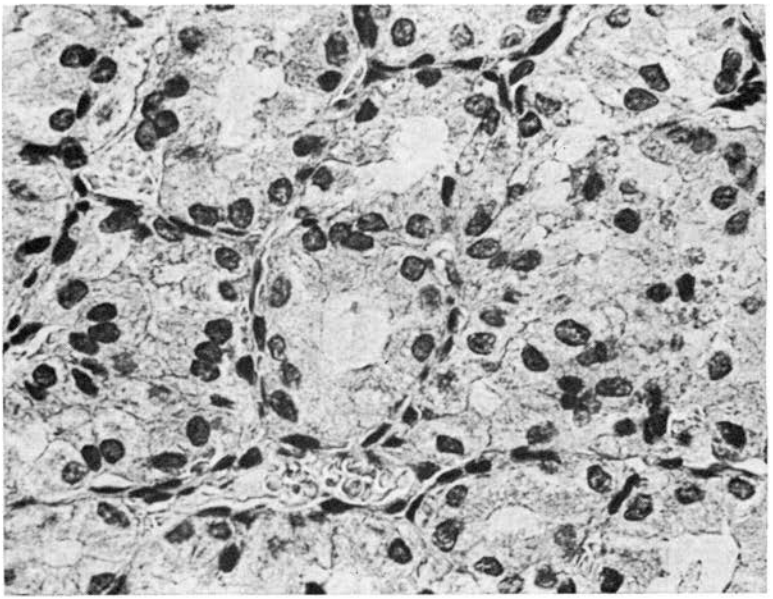

Figure 6. High power field of experimental thyroid. Hematoxylin and Eosin.

previously noted by other investigators (Fregly et al., 1961). Stone et. al. (1951) described an increase of thyroid weight in five of their patients, some of whom began satisfactory recovery on 30 mg. of Tapazole per day.

The striking histological changes noted in the thyroids is due to hyperplasia of the organ and hypertrophy of the cells. This emphasized by the fact that there are approximately twice as many follicles in any given field of the experimental as in the control sections. Hypertrophy of the follicular cells is shown by the change of the cuboidal epithelial cells to low columnar epithelial cells. Since about twice as many follicles were present in any given field in the experimental sections, the width of those follicles is much smaller than that of the control counterparts. The results above verify this.

Because the diameter of the control follicles is greater than the diameter of the experimental follicles and the height of the follicular epithelial cells in the controls is less than its counterpart, the amount of colloid filling the control follicles is greater than the amount within the experimentals. This is again consistent with the results above.

The only unexplainable outcome of the studies of the thyroid was the fact that the epithelial cells lining the controls follicles were greater in number than the others. This cannot be explained in terms of the drug. A possible explanation is that hypertrophy of the follicular cells limits their division.

Several other changes were noticed in the thyroids but these were not measured quantitatively. These changes were concerned with the shape and internal composition of the experimental follicles and with the surrounding connective tissue.

While most of the control follicles were spherical in shape, the follicles in the experimental sections were so tortüous that they varied greatly in shape. Follicles from both groups did contain vacuoles but the colloid in the experimental follicles contained more. Also, there appeared to be more connective tissue and a greater vascular supply around the experimental follicles.

Evidence presented in this paper seems to show that Tapazole is a goitrogenic drug, producing hypertrophy and hyperplasia in rat thyroids. This drug also brings several secondary histological changes along with a general loss of weight in the animal.

ACKNOWLEDGEMENTS

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A Pilot Study of the Thymus of Propylthiouracil-treated Rats[1]

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Abstract. A study of the effects of propylthiouracil[3] on the rat thymus showed histological changes in that tissue. The overall weight of the thymus tissue was reduced in comparison to the thymus weight of the control group. Histologically the thymus of the PTU group showed decreased width in the cortex with fewer lymphocytes and thymic corpuscles in the medullary portion. There appeared to be an intermediate area between the cortex and medulla rather than the distinct demarcation seen between the cortex and medulla of the normal rat thymus.

The results observed in these tissues may indicate a retardation in the maturation of the thymus rather than thymic involution. Further histological studies must be made on the changes of the normal rat thymus from birth to adulthood in order to determine the extent of deviation from normal thymic growth as was observed in this experiment.

BACKGROUND

The theories on function of the thymus and relation to other organs range widely. The major controversy prior to the most recent findings on its autoimmune activity, focused on whether the thymus was a lymphoid structure or an endocrine organ. Recent studies on the thymus have linked it to the autoimmune response in the body and to antibody production. It may also

[1] This research was conducted under the auspices of the Biology Department of Coe College, Cedar Rapids, Iowa.

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[3] 6n propyl-2thiouracil, Nutritional Biochemical Co., Cleveland, Ohio.