Regression of Cardiac Hypertrophy Following Experimental Hyperthyroidism in Rats (35331)

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It is known that the heart hypertrophies during experimental hyperthyroidism. This has been shown in mice (1, 2), rats (3, 4), guinea pigs (5), rabbits (6), and dogs (7). Cardiac hypertrophy may also occur in hyperthyroidism in man. Several observers have reported a tendency for the hearts of lower animals to return to normal size after cessation of administration of thyroid substances. As nearly as we could ascertain, however, only a limited amount of quantitative data has been reported on the exact time it takes the heart to return to normal size following experimental hyperthyroidism. In determining the regression of cardiac hypertrophy in the rat following hyperthyroidism it is important to make observations on each ventricle. It has been shown recently (8) that in experimental hyperthyroidism in the rat the right ventricle hypertrophies proportionally more than the left.

It was deemed worthwhile to make a careful quantitative study of the exact time it takes the heart to return to normal size following experimental hyperthyroidism. Such a study would include partitioning the heart so the time of regression of each ventricle could also be determined.

Methods and Materials. Male rats (weighing about 200 g) of the Sprague-Dawley strain were used; all the animals were young and approximately the same age. The experiment involved 193 animals, 50 controls, and 143 experimentals. They were fed a diet of Purina chow and kept in an air-conditioned room at a temperature of 75°F. The rats were randomly divided into two groups: those receiving daily 0.143 ml/kg of L-3,3′, 5-triiodothyronine (T_3); and the control rats receiving 0.9% sodium chloride solution. The injections were administered subcutaneously for 2 weeks. To check the effectiveness of the hormone action, basal metabolic rates were determined on a substantial number of animals.

To ascertain the average amount of cardiac hypertrophy produced by the administration of T_3, several experimental and control animals were sacrificed the day following the last injection. They were decapitated, the hearts were removed, trimmed, washed with tap water, blotted, and weighed. The hearts were fixed by placing them in a 4% formalin solution for several days. After fixation, the hearts were again weighed to establish a correction factor to compensate for weight changes during the fixation period. The hearts were then partitioned by the method outlined by Keen (9). Each ventricle was weighed separately and the weight was recorded. The remaining animals, both control and experimental, were sacrificed in groups at 3- or 4-day intervals up to a period of 35 days following the termination of the administration of T_3. The hearts of all these animals were treated as were those described above.

The data were subjected to a linear regression analysis (10); statistical analysis was by the *t* test.

Results. The average weight of the control hearts was 1.067 g and that of the experimental group 1.402 g ($p<0.002$). The average cardiac hypertrophy produced by administration of T_3 was 33.11%. The left ventricle was enlarged by 22.97% and the right ventricle, 35.62%, which was statistically significant at the 0.002 level.

To evaluate the results obtained, a linear regression analysis was made of the data. This seemed necessary because the animals

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continued to grow during the course of the experiment, which meant that the heart also became larger. A linear regression analysis would show the amount of cardiac hypertrophy as compared with the gain in heart weight caused by normal growth during the course of the experiment.

The regression of weight upon time for whole heart, left ventricle, and right ventricle are shown in Figs. 1, 2, and 3, respectively. In the regressional analyses the experimental animals were divided into two groups. Group 1 consisted of animals which were sacrificed from the last day of the injections to T_3 to

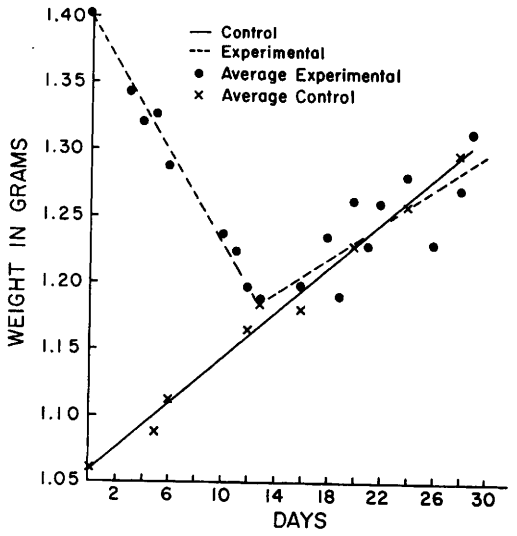

FIG. 1. Whole heart.

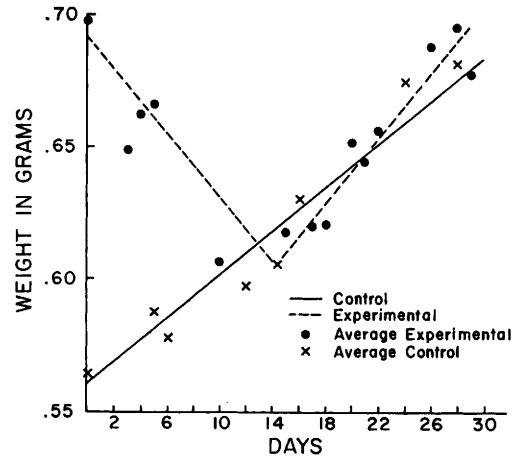

FIG. 2. Left ventricle.

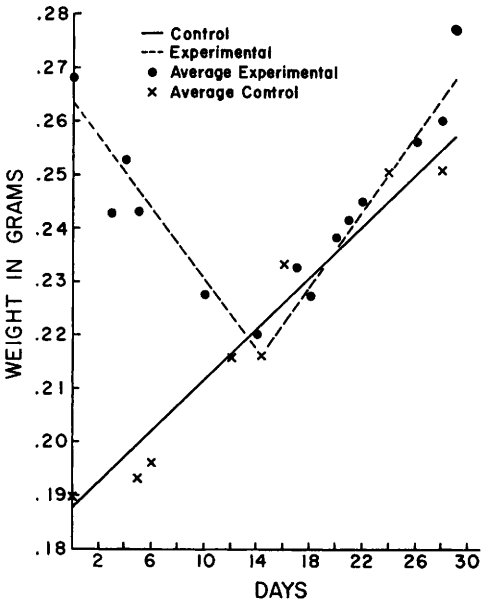

FIG. 3. Right ventricle.

the 16th day; group 2 consisted of animals sacrificed between days 17 and 30. This was done because the data seemed to fall into two linear distributions, one differing from control and having a negative slope from days 0 to 16, and a second coinciding with control and having a positive slope from day 16 onward.

Regression analysis of the data divided in this arbitrary manner indicated that regression of cardiac hypertrophy was complete on day 13; that is, the experimental curve of negative slope intercepted the control curve at day 13. After regression was complete the hearts of the experimental animals showed normal growth. Figures 2 and 3 show that the right and left ventricle behave similarly and reflected the changes seen in the whole heart.

To determine the effectiveness of the thyroid preparation (T_3) the basal metabolism was determined periodically on certain animals randomly selected. The method used was that of Cline and Watts (11). Determinations were made on 15 experimental and 12 control animals. A few days before the animals were sacrificed, the basal metabolism values were 33.5 ± 3.8 and 47.0 ± 7.0 ml of O_2/kg/hr in control and experimental animals, respectively; that is, oxygen consump-

tion was increased 40.2% ($p<0.001$).

Discussion. As early as 1920, Hewitt (12) found that cardiac hypertrophy disappeared when thyroid administration was stopped. However, he did not state how long it took the hearts to regain normal size. In 1958, Gemmill (1) observed that rats and mice which had received T_3 in drinking water showed an average cardiac hypertrophy of 36.7%. He showed this was a true hypertrophy, for the hypertrophied hearts had the same percentage of water content as the normal hearts. Three weeks later a group of these animals still showed a cardiac hypertrophy of approximately 10%. A year later, Sandler and Wilson (4) produced cardiac hypertrophy in rats by administration of thyroxin, and reported that, after withdrawal of the drug, the hearts returned to normal size in about 6 weeks. In 1969, Beznak *et al.* reported that regression of cardiac hypertrophy was complete in 14 days in rats which had been given thyroxine.

Although all these studies have merit, the observations for the main part are not entirely conclusive. The data, for example, presented by Gemmill are not definitive, for he does not state how many of the animals at the end of the 3-week period still showed a significant cardiac hypertrophy, nor did he determine when regression was complete. The data given by Sandler and Wilson are difficult to envisage for they reported that it took 6 weeks for the hearts to return to normal size. This is a considerably longer period than that reported by Beznak *et al.* or by us. The data of Beznak *et al.* are the most exhaustive and are of distinct interest. The work, however, was done on a relatively small group of animals and no linear regression analysis was shown so the step by step process of regression could not be ascertained. Furthermore, the individual ventricles were not studied. The results reported, however, are nearly the same as we are presenting.

There is some evidence that the time it takes for regression of cardiac hypertrophy depends somewhat upon the factor which produced the hypertrophy. For example, Van Liere *et al.* (14), in 1965, reported that cardiac hypertrophy produced by hypoxia did not completely regress until about 3 weeks. In 1969, Bloor and Papadopoulus (15) reported that cardiac hypertrophy produced by exercise in young rats did not regress until 4 weeks. It is difficult to explain these various findings, and presumably more work is needed on cardiac hypertrophy produced by various methods.

It is noteworthy that, after the cessation of administration of T_3, the hearts continued their normal growth, so presumably T_3 did not damage the myocardium. Beznak *et al.* (13) found that cardiac hypertrophy produced by hyperthyroidism shows the most complete regression compared to cardiac hypertrophy produced by other means. They point out that thyroxin probably does not provoke irreversible lesions in the myocardium.

It is rather singular that even though the right ventricle of the experimental animals hypertrophied proportionally more than the left both ventricles had completely regressed between days 13 and 16. It might have been expected the regression of the right ventricle would have taken somewhat longer than that of the left.

Summary. Hyperthyroidism was induced in male, albino rats by subcutaneous injection of T_3 daily for 2 weeks. The day following the last injection, groups of control and experimental animals were killed; the hearts were removed, weighed, and the average amount of cardiac hypertrophy was determined. The hearts were then partitioned and the ventricles were weighed separately. To determine when the hearts returned to normal size, groups of rats were killed at about 5-day intervals up to 35 days. The data were subjected to linear regression analysis. It was observed that the hearts returned to normal size in 13 days; this also held approximately for each ventricle despite the fact that the right ventricle was hypertrophied significantly more, proportionally, than the left ventricle.

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