RELATIVE EFFECTS OF THYROXINE AND SOME OF ITS ANALOGUES ON OXYGEN UPTAKE OF CARDIAC MUSCLE FROM CHICKS

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Submitted to the faculty of the Graduate School of
the Oklahoma State University
in partial fulfillment of the requirements
for the degree of
MASTER OF SCIENCE
August, 1959

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ACKNOWLEDGEMENTS

The writer wishes to express his gratitude to Dr. W. S. Newcomer of the Department of Physiology and Pharmacology for his unlimited interest and helpful guidance during the course of the experiments. Sincere appreciation also is extended to the staff of the Department of Physiology and Pharmacology for their willing assistance and criticisms during the conduction of these experiments and preparation of the thesis manuscript. Gratitude is expressed to the Oklahoma State Heart Association whose financial aid made this study possible. Lastly, the author wishes to acknowledge the help and patience offered by his wife, Mary Jo, and daughter, Sabrina, throughout the entire course of the project.

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INTRODUCTION

The work comparing thyroxine and triiodothyronine in the mammal shows that triiodothyronine is three to seven times as potent as thyroxine in goiter prevention in thiouracil-treated animals, promoting oxygen consumption, increasing tissue metabolism and maintaining growth (Barker, 1955 a). The acetic acid analogue of triiodothyronine gave a faster and greater increase in BMR of the rat than did thyroxine or triiodothyronine; therefore, it was suggested that thyroxine could change into triiodothyronine or their propionic and acetic acid analogues and that one of these compounds could be the hormone that acts at the peripheral tissue level (Gross and Pitt-Rivers, 1953).

In contrast to the vast amount of work which had been reported comparing thyroxine and triiodothyronine in the mammal, less is known concerning the relative potencies of these compounds in the chicken. Shellabarger (1955) compared thyroxine and triiodothyronine in the chicken and concluded that they had equal potencies in preventing thiouracil-induced goiter. He also postulated that possibly a species difference existed as to the manner in which thyroxine and triiodothyronine acted. Newcomer (1957) and Mellen and Wentworth (1959) compared thyroxine and triiodothyronine and found thyroxine to be the more potent compound in preventing thiouracil-induced goiter in the chicken.

Since it appears that thyroxine and triiodothyronine act in the chicken in a manner different from that in the mammal and since no

information is available on the actions of analogues of thyroxine, triiodothyronine, and diiodothyronine, it would be desirable to test the effects of these compounds on an additional target organ in the bird. The purpose of this experiment was to determine the effects of thyroxine, triiodothyronine, diiodothyronine, and their acetic and propionic acid analogues on the oxygen consumption of cardiac tissue of the chicken.

LITERATURE REVIEW

The discovery and identification of 3,5,3', l-triiodothyronine in human plasma (Gross and Pitt-Rivers, 1952) stimulated many investigations into the relationship of triiodothyronine to thyroxine and their propionic and acetic acid analogues in the intact animal.

Gross and Pitt-Rivers (1953) studied the effects of thyroxine, triiodothyronine and their propionic and acetic acid analogues by injecting doses of 0.01 microgram into rats every one to two minutes for three hours and measuring the BMR. The response of the acetic acid analogue of triiodothyronine was greater and much quicker than the response of triiodothyronine and thyroxine; therefore, they suggested that the acetic acid analogue of triiodothyronine could be the peripheral tissue hormone. Gross and Pitt-Rivers also suggested that triiodothyronine and its propionic and acetic acid analogues should be considered as hormones since they gave a response similar to thyroxine but different only in potency.

Lacroix and Leusen (1958) reported that thyroidectomy reduced oxygen uptake of myocardial slices from rats and that injections of thyroxine increased oxygen uptake. Ulrick and Whitehorn (1952) studied the effects of thyroxine on respiration of cardiac tissue and found that rats which were made hyperthyroid from thyroxine given in their feed had a 22% higher uptake of oxygen by the heart ventricles and a 95% higher BMR than did the normal controls. Barker (1955 b) compared the abilities of thyroxine and triiodothyronine to increase oxygen consumption of cardiac tissue in

the rat and found triiodothyronine was four times as potent as thyroxine.

Much work has been reported comparing the potencies of thyroxine and triiodothyronine with reference to their abilities to promote oxygen consumption and BMR of the intact mammal, prevent thiouracil-induced goiter, increase oxygen consumption of tissue slices of various organs of the body and promote growth. A summary and review of these studies can be found in Barker (1955 a). These studies showed that triiodothyronine was three to seven times as potent as thyroxine in the various criteria tested.

In contrast to the abundance of work which has been reported in the mammal comparing the relative potencies of triiodothyronine and thyroxine, little has been reported comparing thyroxine and triiodothyronine in the chicken until Shellabarger (1955) compared thyroxine and triiodothyronine in the chicken using the goiter-prevention technique of Dempsey and Astwood (1943). From this comparison, Shellabarger concluded that thyroxine and triiodothyronine had the same potency in preventing goiter in the chicken. It is possible that different results would have been obtained had more dosage levels been employed in the test, since the response to none of the dosage levels reached that of the normal controls. Shellabarger suggested that possibly a species difference existed and that thyroxine and triiodothyronine acted in a different manner in the mammal as compared to the chicken.

Gilliland and Strudwick (1953) compared thyroxine and triiodothyronine in one-day old chicks using I^{131} and found triiodothyronine to be more potent than thyroxine in preventing the release of the iodine from the thyroid.

Newcomer (1957) studied the relative potencies of thyroxine and triiodothyronine utilizing the Dempsey-Astwood technique in the chicken

and using a variety of criteria of response: heart rate, feather length, oxygen consumption, goiter prevention, and elevation of body temperature. He found that thyroxine was more potent than triiodothyronine in preventing thiouracil-induced goiter but when comparison of thyroxine and triiodothyronine was made to response of oxygen comsumption, feather length, or heart rate, both thyroxine and triiodothyronine had about the same potency. When comparison was made in ability to raise body temperature, triiodothyronine was more potent than thyroxine.

Mellen and Wentworth (1959) compared triiodothyronine and thyroxine in the chicken using I^{131} to measure secretion rate and found thyroxine was more potent than triiodothyronine, thus confirming the work of Newcomer (1957).

Tata and Shellabarger (1959) tested the affinities of thyroxine and triiodothyronine for the blood proteins in the chicken and found the same affinity for binding of both thyroxine and triiodothyronine. They also found that the half-life of thyroxine and triiodothyronine was twenty-two hours. Tata and Shellabarger used this evidence to support the theory that there is no difference in the potency of thyroxine and triiodothyronine in the chicken.

On the basis of the work reported by Shellabarger (1955), Newcomer (1957), and Mellen and Wentworth (1959) comparing the potencies of thyroxine and triiodothyronine in the chicken it would seem that there is a difference in the potencies of thyroxine and triiodothyronine in the chicken as compared to the mammal; however, nothing is known as to the potency of the propionic and acetic acid analogues of thyroxine, triiodothyronine and diiodothyronine.

MATERIALS AND METHODS

White Leghorn cockerels were obtained from the Stillwater Hatchery on the day of hatching and were placed in a battery chick brooder where they received "Superior All-In-One" chicken feed and 0.1% thiouracil in their drinking water for seven to thirteen days. Twelve hours prior to the time of sacrifice, each chick received an intraperitoneal injection of one of the nine compounds used. Mellen and Wentworth (1959), having studied the effects of thyroxine and triiodothyronine on the BMR of the chick, reported that the maximal response was obtained between twelve and eighteen hours after injection. Preliminary trials prior to the initiation of this study substantiated Mellen and Wentworth's results in that maximal oxygen uptake by chick cardiac muscle was obtained twelve to twenty-four hours after injection of thyroxine or triiodothyronine.

Since cardiac tissue from only twenty chicks could be handled in the Warburg apparatus at one time, two or three birds were used at each dosage level along with one normal control and one thiouracil control bird for each "run" in order to minimize experimental variation between dosage groups.

Thyroxine was given in logarithmic doses of 0.01, 0.1, 1, 10, and 100 gamma per 100 grams of body weight (Table I). For special reasons explained in the discussion, one group of ten chickens was injected with 50 gamma of thyroxine. The other eight compounds were given on a molar equivalent basis as compared to thyroxine. Each of the nine compounds was mixed in such a manner that all injections were 0.1 cc. / 100 grams

TABLE I

SCHEDULE FOR THE VARIOUS DOSES OF THYROXINE ADMINISTERED

Volume of Solution Used Per 100 gm. of Body Weight	Molar Concentration of Solution	Moles Per 100 gm. of Body Weight	Total Amount Per 100 gm. of Body Weight; Gamma
0.1 ml.	1.288×10^{-7}	1.288×10^{-8}	0.01
0.1 ml.	1.288×10^{-6}	1.288×10^{-7}	0.1
0.1 ml.	1.288×10^{-5}	1.288×10^{-6}	1.0
0.1 ml.	1.288×10^{-4}	1.288×10^{-5}	10.0
0.1 ml.	1.288×10^{-3}	1.288×10^{-4}	100.0

of body weight. All of the nine compounds used except the acetic and propionic acid analogues of thyroxine were dissolved in a weak solution of NaOH and then diluted to the desired volume with distilled water. The solutions prepared for injection were refrigerated in order to minimize the deterioration of the compounds in an alkaline medium; unused solutions were discarded at the end of three days. The acetic and propionic acid analogues of thyroxine lose their potency if mixed with a weak NaOH solution (Stasilli et al., 1959); therefore, they were dissolved in one part ethyl alcohol and diluted with nine parts propylene glycol.

The chicks were killed by decapitation twelve hours after injection and the ventricles of the heart were removed and placed in an ice-cold phosphate saline solution (Table II) which had been prepared and refrigerated two to three hours previously (Krebs and Eggleston, 1940). The ventricles were removed from the phosphate saline solution and cut into uniform slices of 0.5 mm. in thickness by means of a Stadie-Riggs microtome. Slices of ventricle from the same heart were placed in a Warburg vessel which contained 3 cc. of cold phosphate saline solution. Two-tenths cc. of 10% KOH, together with small strips of filter paper to increase surface, were placed in the center well of the Warburg vessel. The Warburg vessel was mounted to the manometer, flushed with pure oxygen for five minutes, then allowed to equilibrate in the water bath for 15 minutes at a temperature of 37°C. Oxygen uptake readings were taken every 10 minutes for 1 hour at a constant temperature of 37°C.

The slices of ventricle were then removed from the Warburg vessel and dried on a watch glass in an oven at 37°C for 48 hours. The dried ventricle slices were weighed on a Roller-Smith torsion balance. Oxygen uptake was calculated as microliters of oxygen /mg./hr. of dry ventricle.

TABLE II

COMPOSITION OF PHOSPHATE SALINE SOLUTION
(Krebs and Eggleston, 1940)

Volume	Concentration	Compound
1000 ml.	0.9%	NaCL
40 ml.	1.15%	KCL
10 ml.	3.84%	$MgSO_4 7H_2O$
300 ml. of PO_4 buffer adjusted to a pH of 7.4*		

*The buffer was prepared by adding 17.8 gm. of $Na_2HPO_4 2H_2O$ and 20 ml. of .1 N HCL to 1 liter of H_2O and adjusting the solution to a pH of 7.4.

Since the regression of the plotted data involved different levels of a single factor and since the experiment was completely randomized, orthogonal comparisons in regression were made utilizing Snedecor's "F" test to obtain levels of probability (Snedecor, 1956).

The compounds, all of which were the levorotatory form, used in this study and their sources are as follows:

Sigma Chemical Company (purchased)

Thyroxine (free acid)

3,5, Diiodothyronine

Smith, Kline and French Laboratories (gift)

3,5,3', Triiodothyronine sodium (Cytomel)

Warner-Lambert Research Institute (gift)

3,5,3', Triiodothyroacetic acid

3,5,3', Triiodothyropropionic acid

3,3',5,5', Tetraiodothyropropionic acid

3,3',5,5', Tetraiodothyroacetic acid

3,5, Diiodothyroacetic acid

3,5, Diiodothyropropionic acid

RESULTS

The results of the experiments performed to determine the effects of the various treatments on the oxygen consumption of cardiac tissue in the chicken are summarized in Table III (For raw data see Appendix).

Thiouracil reduced the oxygen consumption of cardiac tissue 2.0 microliters /mg/hr. of dry tissue below that of the normal controls (Table III).

When comparing the relative potencies of the nine compounds tested at various dosage levels, all nine compounds exhibited more activity than the thiouracil controls except the propionic acid analogue of diiodothyronine at the 0.1 and 1 gamma levels and diiodothyronine and the acetic analogue at the 0.1 gamma level. These exceptions are not significant since these points are within the standard deviation of the thiouracil control group. Thyroxine gave a greater response than that of any of the other eight compounds at all dosage levels; the response was greater than that of the normal controls at all points tested (Figure 1). The response of thyroxine was significantly different from that of triiodothyronine at all dosage levels (Table IV). Triiodothyronine gave a response greater than that of the normal controls at the 1 and 100 gamma dosage levels (Figure 2). The propionic and acetic acid analogues of triiodothyronine gave responses greater than that of the normal controls at the 100 gamma level (Figure 2). Diiodothyronine and its propionic acid analogue gave responses greater than that of the normal controls only at the 100 gamma level (Figure 3).

TABLE III

MEAN OXYGEN UPTAKE EXPRESSED IN MICROLITERS /MG./HR. OF DRY TISSUE

Compounds	Molar Equivalent Doses (Based on Gammas of Thyroxine)									
	0.01		0.1		1		10		100	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
Thyroxine	6.70	0.64	6.49	0.47	7.36	1.76	8.87	0.79	8.13	0.87
Tetraiodothyroacetic acid	5.79	2.03	5.55	0.24	4.36	0.29	6.13	2.07	5.10	1.55
Tetraiodothyropropionic acid	5.36	1.69	5.49	2.86	5.04	1.45	5.18	0.51	5.45	1.18
Triiodothyronine	4.74	0.55	5.39	0.89	6.45	1.54	5.88	1.40	7.88	1.19
Triiodothyroacetic acid	4.39	0.37	4.10	1.38	4.67	1.36	5.95	1.02	7.03	1.32
Triiodothyropropionic acid	5.01	1.96	5.33	1.77	5.26	1.57	5.61	1.57	6.58	3.05
Diiodothyronine	5.28	1.66	4.68	2.71	4.18	0.75	4.34	0.98	6.98	1.45
Diiodothyroacetic acid	4.95	1.86	5.55	1.60	5.04	1.39	5.03	0.99	5.38	1.35
Diiodothyropropionic acid	5.01	1.96	5.33	1.77	5.26	1.57	5.61	1.57	6.58	3.05

	$\bar{X}$	s
Normal Controls	6.0	.3
Thiouracil Controls	4.2	.3

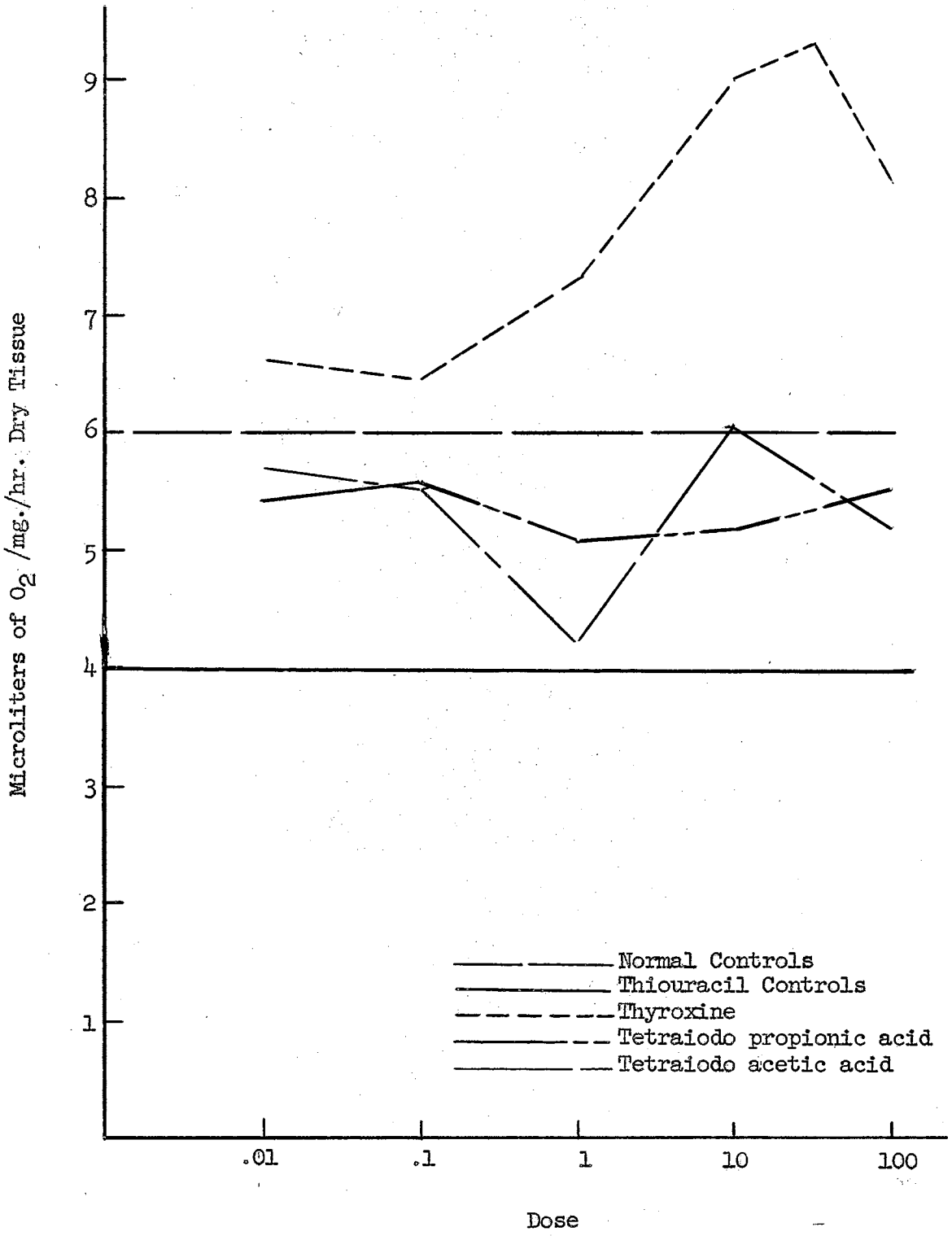

Figure 1. The Responses of Thyroxine and Its propionic and Acetic Acid Analogues

TABLE IV

MEAN SQUARES FOR THE NINE COMPOUNDS TESTED

Compound	Linear Component	Quadratic Component	Cubic Component	Quartic Component	Error
Thyroxine	28.19**	0.01	10.84*	1.77	1.03
Triiodothyronine	45.78**	0.80	4.55	4.51	1.38
Diiodothyronine	9.36*	36.45**	5.74	0.23	2.53
Tetraiodothyropropionic acid	0.02	0.50	0.50	1.72	2.98
Tetraiodothyroacetic acid	0.61	1.38	3.44	13.34**	2.48
Triiodothyropropionic acid	11.70**	2.07	0.99	3.15	4.23
Triiodothyroacetic acid	50.62**	7.75*	1.08	2.17	1.34
Diiodothyropropionic acid	16.84**	21.17**	1.23	0.80	3.47
Diiodothyroacetic acid	0.12	0.01	2.16	1.53	2.17

* = 5% level of probability
** = 1% level of probability

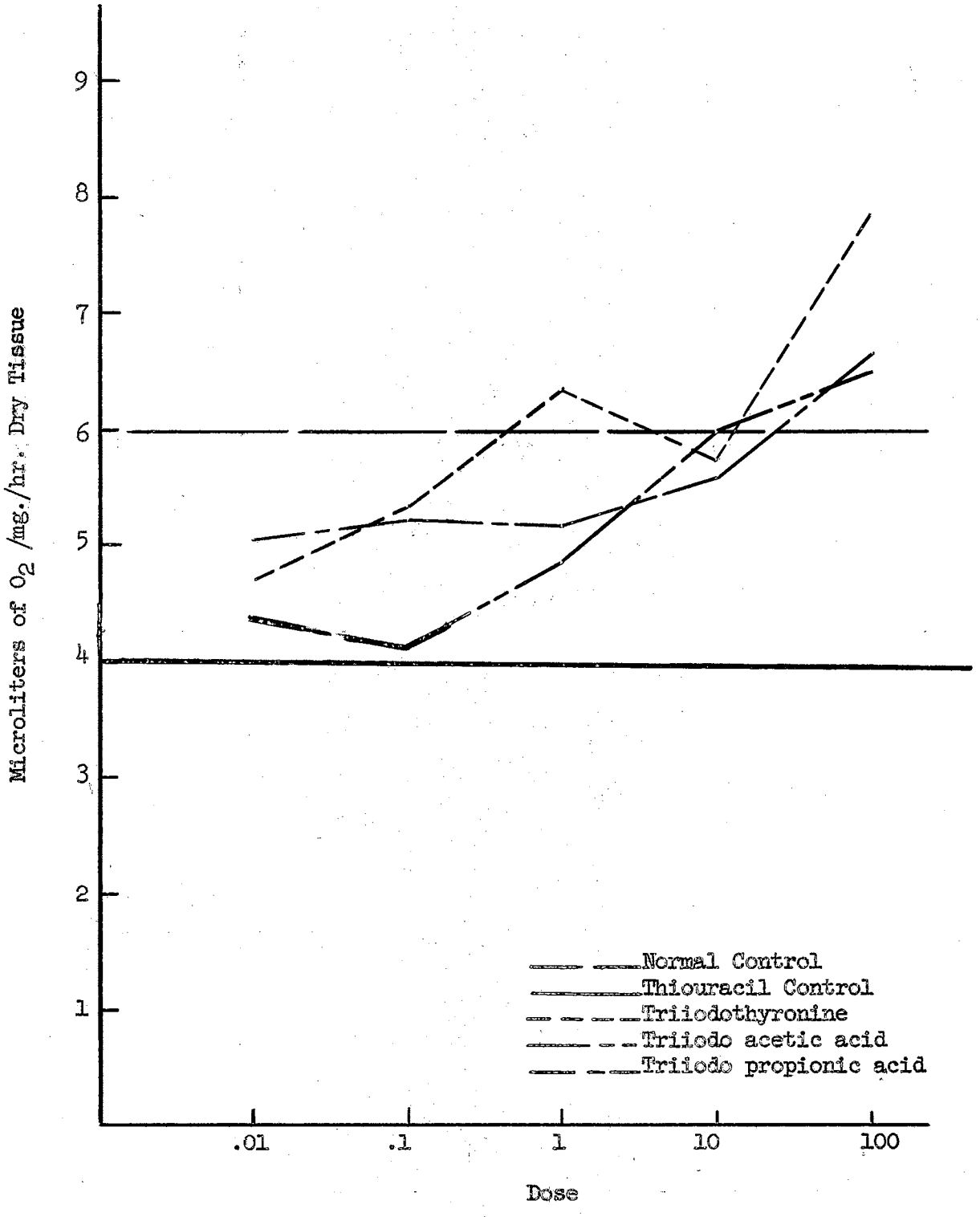

Figure 2. The Responses of Triiodothyronine and Its Propionic and Acetic Acid Analogues

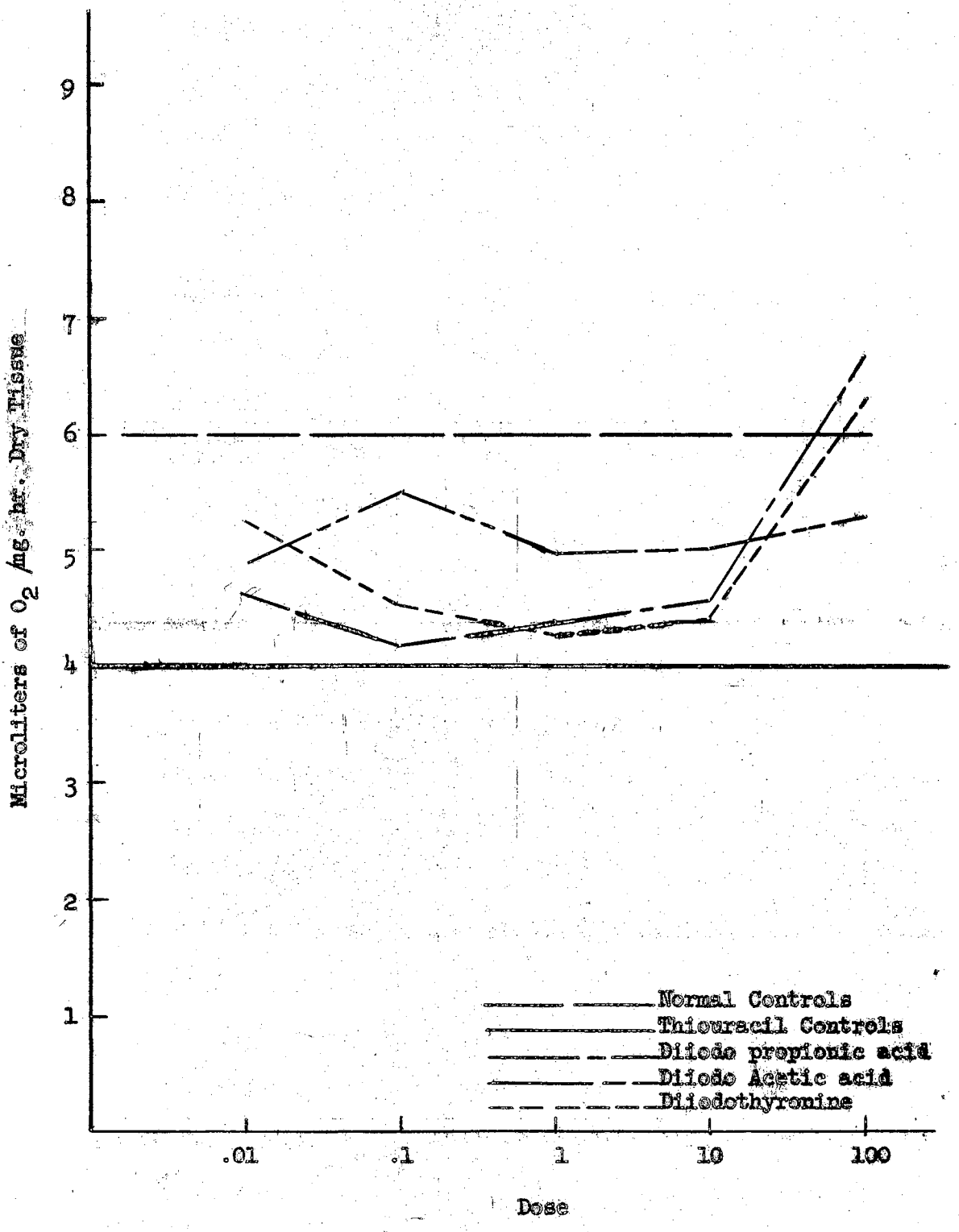

Figure 3. The Responses of Diiodothyronine and Its Propionic and Acetic Analogues

A comparison of the forms of the dose-response curves given by the nine compounds tested was obtained statistically by using an orthogonal comparison in regression since the regression involved different levels of a single factor and the experiment was completely randomized (Snedecor, 1956).

Statistical analysis shows that thyroxine, triiodothyronine, diiodothyronine, triiodothyronine propionic acid, triiodothyronine acetic acid and diiodothyronine acetic acid gave a significant linear response that was proportional to the dose given (Table IV). Analysis also shows that diiodothyronine, triiodothyronine acetic acid and diiodothyronine propionic acid have a quadratic component in their responses. Thyroxine exhibits a cubic response; the acetic acid analogue of thyroxine shows a quartic component in its response (Table IV). The propionic acid analogue of thyroxine and diiodothyronine acetic acid gave linear responses which were not proportional to the dose (Table IV).

DISCUSSION

In the mammal, triiodothyronine is three to seven times more potent than thyroxine. This difference in potencies of these two compounds has been shown using various criteria: preventing thiouracil-induced goiter, increasing oxygen consumption, promoting BMR of the intact animal, etc. (Barker, 1955 a). Triiodothyronine was found to be four times as potent as thyroxine in promoting oxygen consumption of cardiac tissue in the mammal (rat) (Barker, 1956). Since there are a number of different meanings for potency, it is necessary to define what is meant by potency in this study. Potency is based on the magnitude of response using equal molar doses of compounds to be tested at equal intervals after treatment. In the present study thyroxine was more potent than triiodothyronine in promoting oxygen consumption of cardiac tissue in the chicken; therefore, the potencies of triiodothyronine and thyroxine in the chicken are opposite to those which were found in the mammal. The comparison of thyroxine and triiodothyronine in ability to stimulate oxygen consumption of cardiac tissue is in agreement with the results obtained by Newcomer (1957) and Mellen and Wentworth (1959) who reported that thyroxine was more potent than triiodothyronine in preventing thiouracil-induced goiter in the chicken.

When the potencies of thyroxine, triiodothyronine and their acetic and propionic acid analogues were tested in the mammal, the acetic acid analogue of triiodothyronine gave a greater and faster increase in BMR than did thyroxine, triiodothyronine, or their propionic acid analogues.

It was suggested that the acetic acid analogue of triiodothyronine was the peripheral tissue hormone since it caused a greater increase in BRM and oxygen consumption of various tissues in a shorter period of time (Gross and Pitt-Rivers, 1953). In the chicken the propionic acid analogues of triiodothyronine and thyroxine gave greater responses than the acetic acid analogues of triiodothyronine or thyroxine. Since neither the propionic nor acetic acid analogue gave a response as great as triiodothyronine or thyroxine (Figure 1 and 2), it would seem that the acetic acid analogues of triiodothyronine or thyroxine could not be the peripheral tissue hormone in the bird.

The responses of diiodothyronine and its propionic and acetic acid analogues in promoting oxygen consumption of cardiac tissue in the chicken are shown in Figure 4. The dose-response curves for diiodothyronine and its propionic acid analogue are significantly quadratic in form (Table IV). The acetic acid analogue gave a linear response which was not proportional to the dose. Diiodothyronine and its propionic acid analogue were very much alike in response throughout the range tested and particularly from dose levels 1 to 100 gamma.

Comparison of thyroxine and triiodothyronine shows that the dose-response curves of both are nearly parallel at the levels tested and that the response to thyroxine was significantly different from triiodothyronine at the dosage levels tested (Table IV and Figure 4). Statistical analysis of the dose-response curves of thyroxine and triiodothyronine shows that each gave a linear response that was proportional to the dose; however, the response to thyroxine was also cubic (Table IV). In order to obtain more information as to the extent of linearity of the response curve between 10 and 100 gamma, a group of 10 chickens was tested at the 50 gamma level. A mean response of 9.05 microliters /mg./hr. of dry

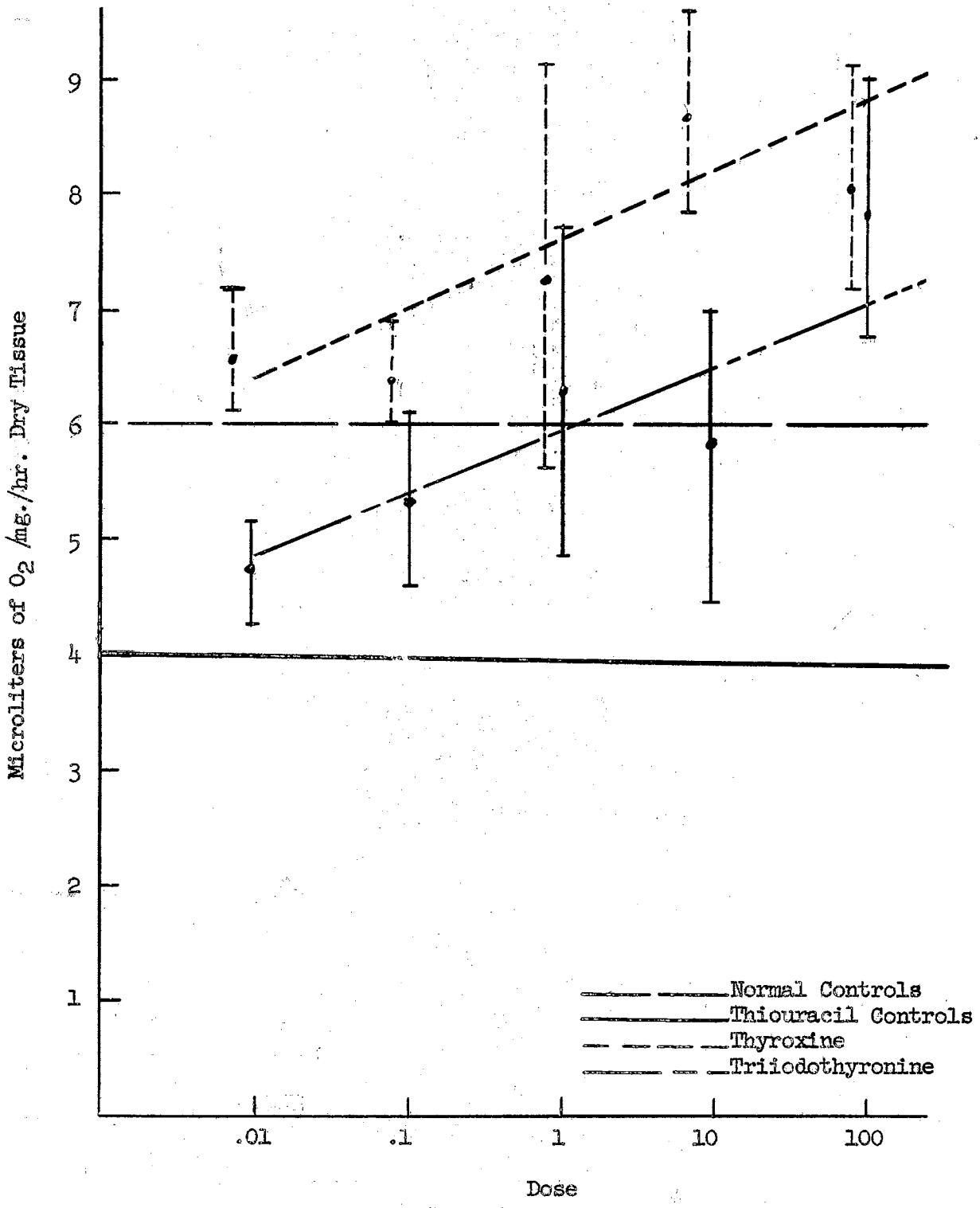

Figure 4. The Regression of Dose to Response for Thyroxine and Triiodothyronine

tissue was found. This is the highest response obtained from any of the nine compounds tested in this study and shows that the response to thyroxine drops beyond the 50 gamma level (Table IV). Since triiodothyronine gave a linear response, it would appear that beyond the 100 gamma level triiodothyronine would become more potent than thyroxine (Table IV and Figure 2).

In examining the dose-response curves of the nine compounds tested in this study, one can see that many of the compounds gave a linear response that was also significantly cubic, quadratic, or quartic. The physiological reason for such responses is not apparent, yet many of these dose-response curves are highly significant.

In searching for a physiological mechanism that would give insight into the different responses that are obtained when comparing thyroxine, triiodothyronine, diiodothyronine and their propionic and acetic acid analogues, many possibilities arise. Thibault (1956) suggested that in the mammal thyroxine changes to triiodothyronine at the tissue level by deiodization and this hormone could enter the cells faster and thereby exert a greater action than thyroxine. Apparently thyroxine does not change to triiodothyronine in the chicken since thyroxine gave a greater response in oxygen consumption of cardiac tissue in the chicken (Table III).

Tata and Shellabarger (1959) found that thyroxine and triiodothyronine were both bound to the globulin fraction of the blood of the chicken with the same affinity; therefore, one could not accept protein binding to be the physiological mechanism whereby a different response is obtained in the chicken and mammal.

The difference in potency of thyroxine and triiodothyronine in the chicken could possibly be explained on the basis of a difference in the affinity of binding sites and/or number of binding sites for thyroxine or triiodothyronine at the target organ. Stetten (1956) presented a method for showing the relationship between hormone dosage and response which was based on the fact that the physiological response to some endocrine products at low dosage levels is proportional to dose and saturation often may be achieved at high dosage levels. By analogy to the Michaelis-Menton concept that the abundance of enzyme-substrate complex limits the velocity of an enzyme-catalysed reaction, it was suggested that the magnitude of a hormone-stimulated response was limited by the abundance of hormone bound to appropriate sites on the target organ. He showed that when dose/response was plotted against dose, a straight line should be obtained with the slope and intercept indicating the capacity of the target organ to bind the hormone and affinity of the hormone for such binding sites respectively. Figure 5 shows the results of plotting dose/response against dose of thyroxine, triiodothyronine, and diiodothyronine in regard to oxygen uptake of cardiac tissue. All three of the compounds gave approximately the same slope and intercept thus indicating that there was no difference in the number of binding sites or affinity of the hormone for the binding site.

The amount of hormone necessary to maintain thyroid weights in thiouracil-treated birds equal to those of normal control White Leghorn cockerels of approximately 2 weeks of age have been found to be 2.45 micrograms per 100 grams of body weight per day (Reineke and Turner, 1945) and 2.9 micrograms for thyroxine and 3.9 micrograms for triiodothyronine (Newcomer, 1957). Data presented in this report shows that 0.01

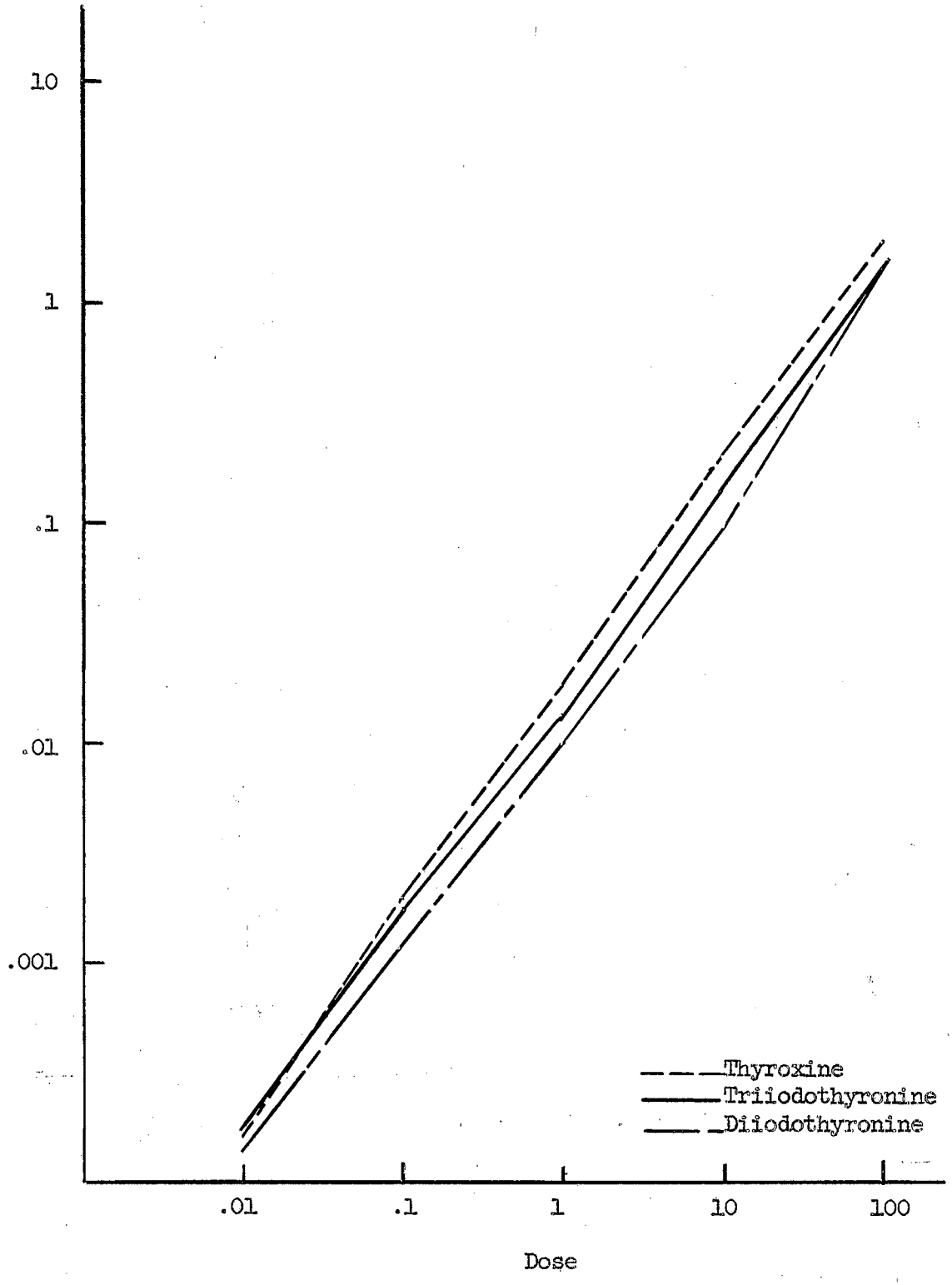

Figure 5. The Regressions of the Dose of Thyroxine, Triiodothyronine, and Diiodothyronine to Dose/Response

micrograms of thyroxine or 1 microgram of triiodothyronine gave an increase in oxygen consumption of cardiac muscle that was greater than the normal controls. A generalized comparison of these figures shows that the heart is 250 to 300 times more sensitive to thyroxine than is the pituitary and that it is 3 to 4 times more sensitive to triiodothyronine than is the pituitary. This greater sensitivity of the heart to thyroxine and triiodothyronine would support Newcomer (1957) and Van Middlesworth (1959) in that the goiter prevention method of Dempsey and Astwood (1943) gives an erroneously high value for the daily secretion rate of thyroxine by the thyroid gland and/or that the thyroid-pituitary relationships are not fully explained by a single feedback mechanism (Goldberg et al. 1957).

It is possible that a difference in the rate of inactivation and/or excretion of thyroxine, triiodothyronine, diiodothyronine or their analogues from the chicken could account for the differences in potency which were obtained when these compounds were compared in the chicken. The only data available are those reported by Tata and Shellabarger (1959) which showed that thyroxine and triiodothyronine both have the same half-life in the chicken. This would indicate that there is no difference in the rate of excretion of thyroxine and triiodothyronine in the chicken.

Since the affinity of hormone to binding sites, number of binding sites on the target organ, rate of excretion, or size of the molecule can not account for the differences in potency which were obtained when thyroxine and triiodothyronine were tested in the chicken, the difference must lie in some other mechanism. Another possibility would be differential permeability of the cell membrane; however, at the present time there is no evidence to support this theory.

SUMMARY AND CONCLUSIONS

The purpose of this experiment was to determine the effects of thyroxine, triiodothyronine, diiodothyronine, and their acetic and propionic acid analogues on the oxygen consumption of cardiac tissue of the chicken.

One-day old White Leghorn cockerels were pretreated with 0.1% thiouracil water for seven to thirteen days. Each chick received an intraperitoneal injection of one of the nine thyroid analogues twelve hours prior to the time they were sacrificed. Thyroxine was given in logarithmic doses of 0.01, 0.1, 1, 10, and 100 gamma per 100 grams of body weight and the eight other compounds were given on a molar equivalent basis as compared to thyroxine. Oxygen uptake of the cardiac tissue was measured using the Warburg apparatus.

Thiouracil treatment lowered the oxygen uptake 2.0 microliters below that of the normal controls. When comparing the relative potencies of the nine compounds tested at various dosage levels, all nine compounds tested exhibited more activity than the thiouracil controls. Thyroxine gave a greater response than any of the other eight compounds at all levels; the response was greater than that of the normal controls at all points tested. Triiodothyronine was the second most active compound when compared at the 0.1 to the 100 gamma dosage levels. The remaining compounds, in general, did not exceed the response of the normal controls except at the 100 gamma level.

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APPENDIX

RAW DATA

OXYGEN CONSUMPTION OF CARDIAC TISSUE AT VARIOUS DOSAGE LEVELS OF THYROXINE AND ITS ANALOGUES

Compound	.01 Gamma	.1 Gamma	1 Gamma	10 Gamma	100 Gamma
Thyroxine	7.92	6.07	11.57	7.99	6.03
	6.95	6.84	5.79	8.88	8.06
	6.86	7.04	7.32	8.10	8.61
	5.81	6.55	7.29	7.77	7.69
	7.21	6.03	4.67	9.07	9.24
	5.76	5.79	6.96	10.14	7.91
	6.37	6.81	7.64	9.01	8.45
	6.42	6.72	6.79	8.88	8.85
	6.72	7.02	6.93	8.79	8.09
	6.67	6.01	6.87	10.04	8.41
	$\bar{X}$ 6.70±.64	6.49±.47	7.36±1.76	8.87±.79	8.13±.872
	(See the end for 50 gamma level of thyroxine)				
Triiodothyronine	4.21	4.61	5.70	7.89	8.84
	4.31	4.92	5.67	5.47	8.85
	4.96	4.76	4.87	7.80	9.24
	4.54	7.74	4.60	4.95	5.81
	5.71	5.09	6.96	6.78	5.82
	4.59	5.36	8.62	3.84	7.87
	4.57	5.82	7.79	4.09	7.92
	4.23	5.13	4.58	5.38	7.90
	4.59	5.36	7.79	6.11	7.80
	5.71	5.09	7.96	6.53	8.72
	$\bar{X}$ 4.74±.55	5.39±.89	6.45±1.54	5.88±1.40	7.88±1.19
Diiodothyronine	5.41	2.15	3.92	3.63	10.55
	3.92	4.28	3.58	5.11	6.96
	8.82	5.69	5.71	6.02	6.29
	7.07	4.00	3.46	3.33	6.25
	4.10	11.41	3.58	4.16	8.25
	3.70	4.17	3.88	3.73	5.74
	6.09	3.79	3.99	5.60	5.96

Compound	.01 Gamma	.1 Gamma	1 Gamma	10 Gamma	100 Gamma
Diiodothyronine	3.81	3.39	5.02	3.47	6.04
	4.54	3.87	4.77	4.69	6.90
	5.32	4.06	3.88	3.11	6.87
	$\bar{X}$ 5.28±1.66	4.68±2.71	4.18±0.75	4.34±0.98	6.98±1.45
Triiodothyro-acetic acid	4.53	3.92	4.47	5.00	5.66
	4.83	3.83	4.62	4.50	6.65
	3.88	3.89	3.30	5.34	7.72
	4.65	4.30	3.18	5.33	9.61
	3.89	2.59	6.11	7.85	5.60
	4.59	7.18	6.79	6.82	6.21
	4.81	2.23	2.75	6.82	5.99
	3.91	5.34	6.16	5.36	7.88
	4.56	3.76	4.51	6.42	8.43
	4.24	4.02	4.80	6.01	6.52
	$\bar{X}$ 4.39±0.37	4.10±1.38	4.67±1.36	5.95±1.02	7.03±1.32
Triiodothyro-propionic acid	6.36	9.23	7.53	6.49	3.59
	6.28	7.31	7.48	6.13	8.25
	9.75	3.17	3.90	8.91	5.28
	3.67	4.78	4.81	4.25	3.43
	4.12	5.63	4.31	4.40	6.23
	3.41	5.07	4.16	4.69	4.39
	4.40	3.77	6.34	3.66	4.77
	4.52	4.98	4.72	4.91	13.30
	3.70	5.21	4.44	5.72	8.71
	3.89	4.11	4.97	6.97	7.82
	$\bar{X}$ 5.01±1.96	5.33±1.77	5.26±1.57	5.61±1.57	6.58±3.05
Diiodothyro-propionic acid	9.70	2.65	6.22	6.93	6.28
	7.50	5.89	3.22	5.35	4.63
	4.48	6.29	6.36	4.88	7.26
	2.71	3.23	2.47	2.98	10.17
	4.03	1.99	1.88	3.35	5.50
	3.08	3.14	4.50	3.31	3.75
	1.57	3.51	4.09	3.72	8.43
	6.59	6.39	3.51	2.73	4.19
	3.07	3.71	4.71	4.44	7.64
	3.82	3.82	5.04	6.71	7.33
	$\bar{X}$ 4.66±2.51	4.06±1.57	4.20±1.48	4.44±1.51	6.52±2.03

Compound	.01 Gamma	.1 Gamma	1 Gamma	10 Gamma	100 Gamma
Diiodothyro-acetic acid	2.43	3.68	4.45	5.75	6.25
	7.66	6.32	4.48	3.89	4.37
	3.32	4.49	5.34	5.46	5.17
	6.21	7.74	7.86	7.23	7.65
	7.55	6.49	5.73	4.82	5.59
	5.54	8.27	3.30	5.07	4.49
	4.43	3.82	3.26	4.95	3.89
	4.98	4.62	4.17	5.02	4.16
	2.57	5.43	5.72	4.26	7.61
	4.81	4.62	6.04	3.83	4.62
	$\bar{X}$ 4.95±1.86	5.55±1.60	5.04±1.39	5.03±.99	5.38±1.35
Tetraiodothyro-propionic acid	4.26	3.67	5.84	4.91	4.27
	5.11	4.06	4.72	4.89	4.96
	8.06	13.11	4.15	4.72	6.30
	7.56	6.20	6.89	5.95	3.94
	5.31	5.22	6.24	6.02	4.33
	7.34	6.34	7.12	4.69	5.77
	4.11	3.21	5.21	5.00	7.81
	3.24	4.34	2.99	5.19	6.31
	4.07	3.99	4.09	5.66	5.79
	4.51	4.76	3.24	4.77	4.97
	$\bar{X}$ 5.36±1.69	5.49±2.86	5.04±1.45	5.18±.51	5.45±1.18
Tetraiodothyro-acetic acid	10.57	5.16	4.24	5.51	3.66
	3.84	5.16	3.77	4.58	4.86
	4.20	4.42	4.75	4.99	5.06
	4.33	5.49	6.38	8.45	4.93
	6.43	4.80	3.21	10.99	2.91
	5.66	5.91	3.33	5.03	4.03
	4.84	6.39	3.89	4.54	6.98
	7.60	5.08	4.27	5.61	8.16
	4.72	6.97	4.67	6.63	4.37
	5.68	6.07	5.07	4.97	6.07
	X 5.79±2.03	5.55±0.24	4.36±0.29	6.13±2.07	5.10±1.55

Normal Controls

5.46	5.41	6.73	5.79
5.40	5.37	5.37	6.07
7.02	7.04	5.92	7.01
6.87	6.88	5.27	6.04
6.09	6.04	5.87	5.42
6.73	5.41	5.35	5.82
5.41	5.92	7.02	6.08
5.23	5.27	6.84	6.77
5.98	5.81	5.42	5.81
5.81	6.71	5.77	5.92

$\bar{X}$ 6.0±.30

Thiouracil	Thyroxine 50 Gamma
3.50	8.17
4.25	10.57
3.93	8.69
3.82	7.81
4.01	8.12
3.76	7.07
4.23	11.88
4.50	7.94
4.50	8.67
3.51	11.44
$\bar{X}$ 4.00±.30	9.04±.52

VITA

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