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To Gale

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INTRODUCTION:

The interrelationship of the thyroid gland and the cardiovascular system has been known since the early nineteenth century. Hyperthyroidism, by increasing oxygen consumption, can cause an almost concomitant rise in cardiac output. The arterial pulse pressure in hyperthyroidism is increased because of an elevation of systolic pressure and a decrease in peripheral resistance.

Interest in the relationship between the thyroid and hypertension, therefore, was natural following the description by Goldblatt et al (1934) of a mechanism for the production of persistent elevation of systolic blood pressure by means of renal ischemia in dogs.

1) Hypertensive Studies in Dogs:

Page and Sweet (1937), confirmed by Braun-Menendez (1952), showed that dessicated thyroid (0.8 Grams) raised moderately the pressure of hypertensive dogs whose pressure had previously been reduced by hypophysectomy. Glenn and Lasher (1938), however, using the Goldblatt clamp, found that thyroidectomy caused no significant fall in blood pressure and that the application of the clamp after thyroidectomy was followed by a well sustained rise in the dogs' blood pressure. Blood cholesterol was used as an index of severity of myxedema. These findings were confirmed by Katz et al (1939).

Page and Sweet (1937) had postulated that the responsiveness of blood vessels to chemical stimuli from the kidney was secondary to an increase or decrease of thyroid or adrenal secretions. Testing the effect of the athyroid state on vascular reactivity and arterial pressure in renal hypertensive dogs, Page and McCubbin (1952) showed that vascular responsiveness to epinephrine, norepinephrine, renin and angiotensin was

reduced with suppression of thyroid function in normotensive dogs. The possibility that suppression of thyroid function in renal hypertensive animals might be associated with a decrease in arterial blood pressure was not confirmed (McCubbin and Page, 1952) and changes of vascular reactivity were slight in comparison with those of normotensive dogs.

Eleven out of seventeen dogs with Goldblatt hypertension were found by Wakerlin et al (1957) to have a decrease in systolic blood pressure when fed diets containing thiouracil and rich in cholesterol. How much of the fall was due to either of the substances singly was unclear because when given individually neither had an effect on the two hypertensive dogs on each treatment.

Brull and Op de Beek (unpublished) observed no increase in basal metobolic rate in dogs made hypertensive by the Goldblatt technique. Brull and Merchie (1958), however, found a progressive increase in thyroid activity (protein bound iodine) in renal hypertensive dogs. The PBI was greater later in the course of the experiment than earlier despite the progressive decrease of blood pressure at the end. The technique used in these experiments was unilateral nephrectomy and clamping of the contralateral renal artery. How much significance may be attached to the increased PBI is undetermined since nephrectomy alone is a stimulus for increased thyroid secretion.

On the basis of the experiments performed on dogs, the thyroid gland would seem to play no important role in either the maintenance or genesis of renal hypertension. This does not mean that there does not exist a close relationship between the thyroid and experimental renal hypertension in other animals; and indeed this has been shown to be true in the rat.

2) Hypertensive Studies in Rats:

Wastl (1945) studied the influence of two thiourea derivatives on blood pressure in hypertensive rats. The substances used caused a decrease in blood pressure in hypertensive rats but not in normals. The blood pressure drop occurred during four days of intraperitoneal injections and returned to preinjection levels within four days. Although response was said to vary with the dose, it is puzzling that the antithyroid effect should have been achieved so rapidly.

Bachtold (1950) found that methyl-thiouracil had no influence on the blood pressure of normal rats, but that it decreased blood pressure in renal hypertensive rats only during the course of treatment. Similarly treatment before hypertension was produced only delayed the appearance of hypertension.

Thyroxine at a dose of 10 mg per kg per os or 1 mg per kg s.q. caused a rise in blood pressure in normal animals from 110 to 142 in two weeks and then a decline to 124 after eight weeks, at which time treatment was ended. After thirteen weeks, the blood pressure was back to normal. In hypertensive animals, the blood pressure was elevated from 170 to greater than 230, leading to death. Thyroxine also prevented the decrease of blood pressure in hypertensive rats treated with methyl-thiouracil.

In animals subjected to figure-of-eight ligature of one kidney and extirpation of the other, given 1% saline to drink, thyroidectomy or thiouracil decreased hypertensive blood pressure levels almost to normal (Braun-Menendez, 1954). In rats with moderate reduction in renal mass, that is ligature alone, thiouracil reduced the slight

hypertension almost to normal. Thyroid powder (15-25 mg per day) or thyroxine (40 µg s.q. per day) increased the blood pressure of normotensive animals with moderate renal mass reduction, and with some persistence of the increased blood pressure after therapy.

Braun-Menendez and Penhos (1955) found that thyrotropic hormone raised blood pressure in normotensive or moderately hypertensive rats with reduced renal mass, causing a rise to hypertensive levels. The effect was not observed in thyroidectomized animals.

Using high doses of tri-iodo-thyronine, Zadunaisky (1957, 1960) showed no increase in the blood pressure of normal rats but an increase in those rats with reduced renal mass (unilateral nephrectomy, figure-of-eight ligature and 1% saline to drink) during the silent period before hypertension developed. The test of radioactive iodine uptake by the thyroid gland after 24 hours in stable hypertensive and normotensive control animals showed no appreciable difference. This would implicate the thyroid in the developmental period of hypertension.

Osorio (1956) testing vascular reactivity in normal, hypo- and hyperthyroid rats found that rats treated with thyroid powder showed slightly less sensitivity to pressor drugs than normals. The decreased sensitivity of the hypothyroid group was greater. When the hypothryoid group was treated with vasodepressors they were more sensitive than the normals. This latter finding is in agreement with that of Page and McCubbin (1952) in dogs.

A short communication by Martin and Lehr (1955) reported that thyroid-parathyroidectomy in rats with renal obstruction delayed the emergence of hypertension.

Krieger (1956) discovered that thyroid powder (30 mg per day per os, equal to approximately 117 µg thyroxine*) caused no increase in

blood pressure in normal rats over a period of three weeks, whereas the same treatment in rats with reduced renal mass(figure-of-eight ligature and unilateral nephrectomy) caused a significant rise in blood pressure. 2-4 Dinitrophenol had no renotrophic or hypertensive effect although it shared with thyroxine an augmentation of oxygen consumption.

Recently Fregly and his colleagues (Fregly, 1958; Fregly and Hood, 1959; and Fregly, Baker and Gennaro, 1960) have explored the effects of propyl-thiouracil, as well as thyroidectomy, in the development and maintenance of renal hypertension in rats. PTU prevented or removed hypertension associated with bilateral kidney encapsulation with latex envelopes; however, the effect was not permanent. This treatment also decreased blood pressure in normal non-encapsulated rats. The systolic blood pressure of established hypertensive females was not significantly effected by surgical thyroid-parathyroidectomy; although this treatment did prevent a rise in blood pressure to hypertensive levels. As with PTU, thyroid-parathyroidectomy reduced blood pressure in normal unoperated controls. PTU could not decrease further the blood pressure of thyroid-parathyroidectomized rats over a long period of time, although there was an early transient decrease.

Fregly and Cook (1960) confirmed earlier work that the antithyroid drugs, thiouracil, propylthiouracil and methimazole, prevented both the development of increased blood pressure and cardiac hypertrophy which usually accompanied kidney encapsulation with latex envelopes. The drugs also reduced the increased blood pressure in rats with hypertension of 13 to 40 weeks duration prior to drug administration. Addition of dessicated thyroid powder to the diet containing the antithyroid drug overcame the antihypertensive effect of the latter.

*Pharmacopea Aregentina

Withdrawal of thyroid powder was followed by return of the blood pressure to previous low levels. The anti-hypertensive effect of the antithyroid drugs was attributed to decreased thyroid secretion rathar than the extrathyroidal effects of the antithyroid drugs, eg. decreased food intake, anemia, polydipsia, etc.

Thyroid activity as assessed by the ratio of thyroid weight to body weight, precipitate to serum I^{131} ratio, and mean thyroid acinar cell height, increased sharply as the systolic blood pressure approached the high normal or low hypertensive range (Fregly and Gonzales 1961).

The differences shown by dogs and rats may perhaps be explained by the fact that although minor degrees of clinical hypothyroidism can be produced readily in dogs, myxedema is rare. The dog is unusual in that it is relatively insensitive to both excess and deficit of thyroidal hormone. Brewster et al (1954) found no significant increase in mean arterial blood pressure in dogs fed 0.8 grams per kilogram of thyroid for a period of three weeks, (compare with Page and Sweet 1937).

The work that has been done in Europe by Wastl and Bachtold, in South America by Braun-Menendez, Penhos, Osorio and Zadunaisky and in the United States by Fregly would clearly indicate the existance of a relationship between the genesis of experimental renal hypertension in rats by the Goldblatt and related techniques and thyroid function. Decrease in thyroid function does not prevent the occurrence of hypertension. The effect of the thyroid on maintenance of established renal hypertension would seem of less importance.

In addition to the Goldblatt technique, experimental hypertension has been established by chronic administration of corticosteroids in large doses or in smaller doses by concomitant administrations of saline

and/or renal injury. Selye (1950) showed that thyroxine at a dose of 2 mg per day might be substituted for desoxycorticosterone acetate in the production of nephrosclerosis and hypertension by a combination of DOCA, 1% saline as drinking water and unilateral nephrectomy.

The Thyroid in Metacorticoid Hypertension

Selye (1953) determined that thyroidectomy protected considerably but incompletely against the toxic effects of DOCA. In particular it decreased the power of DOCA to produce hypertension. Thyroxine (Selye and Bois, 1956) was shown to act as a sensitizing agent in the production of renal and cardiovascular lesions with steroids.

Hypophysectomy inhibited all the manifestations of DOCA overdosage (Salgado and Selye, 1953), but the effects of thyroidectomy were nearly as complete. Thyroidectomy at the beginning of DOCA treatment (Salgado and Green, 1956; Salgado, 1953) prevented hypertension, but after the establishment of DOCA hypertension, its effect was only short lived. Thyroid-parathyroidectomy (Salgado and Selye, 1954) had a dissociative effect on the cardiovascular and renal changes caused by methyl androstenediol, inhibiting the production of hypertension. The effects of thiouracil (Salgado, 1954) were found to be similar to thyroidectomy.

The significance of steroid hypertension has been debated because of the extreme conditions, i.e. the high dose of steroids, necessary to produce it. It would be safe to conclude, however, as did Green et al (1952) and Salgado and Green (1957), that the thyroid might play a significant role in the development of DOCA hypertension. Suppression of thyroid function did not favorably influence established DOCA hypertension.

Mechanisms of Thyroid Action in Renal Hypertension

1) Vascular Reactivity

2) Direct Effect: Kidney Growth and Function

3) Indirect Effect: Mediated Through the Adrenals

4) The Renotropin Hypothesis

1) Vascular Reactivity

A frequently discussed possibility is that the thyroid hormone acts on the calibre of the renal vessels either directly or through a change of vascular reactivity to various pressor agents. Sawyer and Brown (1935) and Aumann et al (1940) found an altered sensitization of the adrenergic neuroeffector systems by the thyroid hormone. They found no increase in medullary output secondary to hyperthyroidism. Brewster(1954) discovered that the cardiovascular effects of thyrotoxicosis were not due to the direct effect of thyroxine per se but rather to an augmentation of the physiological effects of epinephrine and norepinephrine by thyroxine. The changes produced by increased concentrations of thyroid hormone were abolished by preventing the reflex release of epinephrine and norepinephrine with a total sympathetic block. (Brewster et al 1956). Roskowski (1956) discovered that medial necrosis produced by large i.v. injections of epinephrine was not produced in thyroidectomized animals.

Page and McCubbin (1952) found that vascular responsiveness to a variety of pressor and depressor drugs in dogs was in some degree

dependent on thyroid activity. Thyroidectomy suppressed vascular reactivity to a number of substances in normal animals but had little or no effect in established hypertension. Osorio (1956) found that rats treated with thyroid powder showed a little less sensitivity to pressor drugs when compared with normals and the hypothyroid animals showed a considerable decrease in sensitivity. The decrease was quite marked in hypothyroids treated with depressor substances.

The experiments on vascular reactivity tend to show differences in vessel reactivity in normal or early hypertensives to that in established hypertensives. These results are in agreement with those which demonstrate a greater and more prolonged reaction of blood pressure to various treatments in animals which are in the silent period preceding hypertension or already have mild early hypertension.

2. Direct Effect: Kidney Growth and Function

The positive effect of the thyroid on kidney growth is well known (Iscovesco, 1913; Hoskin, 1910, 1916; Hewitt, 1920; quoted in Cameron 1920. This renotrophic activity was shown by Swann (1939) to be present in the absence of the pituitary. Antithyroid drugs were discovered to produce a decrease in renal weight (Cottet et al, 1951).

Unilateral nephrectomy caused an increase in thyroid secretion (Brull and Merchie, 1958); and thyroxine (Dragoni, 1952) increased compensatory renal hypertrophy in normal rats, although thyroidectomy did not completely prevent such hypertrophy (Zeckwer et al, 1946). The thyroid-pituitary axis was proved relatively unimportant since hypophysectomy did not prevent compensatory renal hypertrophy (Braun-Menendez and H.E.J. Houssay, 1959).

Ogawa (1958) found a mitosis stimulating factor in the serum of unilateral nephrectomized rats. Mandel et al (1953) working on experimental nephritis showed that thyroxine favored cell repair.

Fateeva (quoted in Brull and Merchie, 1958), using I^{131} uptake, and Brull and Merchie (1958), using PBI, demonstrated an increase in thyroid secretion to renal ischemia. Albright et al (1954), among others, had shown that kidney slices could metabolize thyroxine to triiodo-thyronine; and using time reponse tissue studies in thyroxine injected rats, Barker and Klitguard (1952) found that no tissue was specifically dependent on another to increase its energy metabolism turn-over in response to thyroxine. Since 2, 4-dinitrophenol shared with thyroxine its actions on oxygen consumption but not on kidney growth, Krieger (1956) could postulate that the hypertensive effect of thyroxine was due to its renotrophic action. Dumont (1943) showed that ischemia of transplanted cervical kidneys pretreated with thyroxine yielded a greater increase in blood pressure than did ischemia of transplanted normal kidney.

3. Indirect Effect: Mediated Through the Adrenals

Favoring an indirect mechanism for thyroid action in renal hypertension, Selye (1950, 1953) and Salgado andSelye (1954) proposed that thyroxine produced kidney lesions and hypertension by means of an increased production of mineralocorticoids. Thyroidectomy decreased adrenalcorticoid production.

Green et al (1952) and Fregly and his co-workers (1958-60) maintained that certain forms of experimental hypertension did not involve

adrenal cortical activity and that propylthiouracil's effect on blood pressure was not due to hypofunction of the adrenals. Fregly was able to obtain renal hypertension in the face of bilateral adrenalectomy, confirming earlier work by Fasciolo, 1938.

Several authors (Bauman and Marine, 1945; Deane and Greep, 1947; Freedman and Gordon, 1950; Farrow and Money, 1949), however, found that propylthiouracil or thyroidectomy decreased adrenal size. But Rosenfield (1952) showed that thyroxine added to artificial perfusate of calf adrenals gave no acute increase or decrease in adrenal cortical activity. Chappel et al (1958) demonstrated that the weights of adrenals of PTU treated animals were not significantly less than hypertensives when expressed in terms of body weight, but a definite histological difference, i.e. shrinking of the zona fasciculata was seen. This latter finding confirmed the work of Deane and Greep (1947). Whether this was an effect of changed ACTH secretion or direct action of thyroxine is not known. Martin (1955) wrote of a lack of substantial adrenal hypertrophy following obstruction nephropathy in thyroid-parathyroidectomized dogs.

In a recent work on the thyroid gland in the development and maintenance of renal hypertension (Fregly and Cook, 1960) the increase in thymus weight ratio which usually accompanied adrenal hypofunction failed to manifest itself after treatment with antithyroid drugs. There was also no observed difference with respect to adrenal cholesterol concentration between encapsulated and non-encapsulated kidneys of propylthiouracil treated rats.

4) The Renotropin Hypothesis

Braun-Menendez (1952, 1958) sought to bring together all work on experimental renal hypertension by postulating the existence of a substance probably connected with intermediary metabolism. He suggested that the kidney existed in a relationship between certain demands which the body might impose and its capacity to respond to them. For example, the adrenals responded to ACTH and the thyroid to TSH. This substance or group of substances, which has not been isolated, regulated kidney growth and function and was named Renotropin. Its rate of production increased under the influence of hormones of the anterior pituitary, gonads and thyroid. Normally there existed an equilibrium between the production of Renotropin and its destruction, transformation or utilization by the kidney, Increase of Renotropin caused kidney hypertrophy and decrease led to atrophy. When the equilibrium was disrupted and the remaining kidney tissue was unable to respond to the stimulus of normal or increased amounts of Renotropin present in the blood, hypertension developed. The mechanism whereby hypertension results is unknown, although it may be through secretion of renin.

According to the Renotropin Hypothesis any of several hormones and a high protein diet were capable of interrupting the equilibrium between Renotropin production and a kidney unable to respond by reason of a figure-of-eight ligature, thus causing an increase in blood pressure. Because most of the body's hormones and diet exerted an influence on blood pressure of renal ischemic origin, Braun-Menendez felt that these effects were exerted through intermediary metabolism.

Recently Toth and Bartfai (1960), after establishing renal ischemic hypertension in parabiotic rats, were able to show an antihypertensive effect in the plasma of the rat with intact kidneys.

Herlant (1949) showed that excess protein or thyroid treatment caused their greatest hypertrophy in the brush segment of the nephron where absorption of glucose and other metabolites occurs. The effect of the thyroid was secondary to its increasing of substances such as glucose in the blood stream and its greater reabsorption of such substances by virtue of its hypertrophic response on the nephron.

Hoffman et al (1948) showed that adrenalectomy decreased oxygen consumption in rats by 10%. Adrenalectomy and thyroidectomy decreased oxygen consumption by 20%. The effect of thyroxine on metabolic rate was decreased in adrenalectomized rats. Administration of cortical extract to adrenalectomized rats allowed a normal metabolic response to thyroxine. Hoffman et al (1949 a b) found that thyroxine injected adrenalectomized rats did not show the elevation of urinary nitrogen observed in the controls. This was also observed in rats adrenal-ectomized following thyroid therapy. If increased urinary nitrogen was taken as a measure of increased protein metabolism, then the adrenalectomized rat was incapable of participating in the usual metabolic acceleration induced by thyroxine.

Handler and Bernhein (1951) studying the effects of caloric restriction and the role of the adrenals in renal hypertension showed a decrease in blood pressure in animals fed a low protein diet and a restoration of the blood pressure by administration of ACTH or

thyroid powder.

The experiments of Herlant, Hoffman and Handler, although by no means definitive, would tend to support a unifying hypothesis such as that of Braun-Menendez in regard to the relationship between intermediary metabolism and renal hypertension.

The experiments reported in this paper were undertaken to further delineate the interrelationship of the thyroid and adrenal glands in experimental renal hypertension, especially during the silent period after the reduction of renal mass and before the appearance of hypertension. This is the period when most of the factors concerned with the production of hypertension would seem to be most active.

Materials and Methods:

White Male rats of the Institute strain were used except for Experiment 5 where white male Wistar rats from the Argentine Atomic Energy Commission were employed. All animals were kept on the standard chow diet of the Institure. Tap water was given ad lib; during the course of the experiments this was changed to 1% saline. In several experiments the saline consumption during the elapsed period was measured.

Blood pressure was determined using the plethysmographic technique of Williams, Harrison and Grollman (1939), slightly modified and using light ether anesthesia, Fig 1. Each animal's blood pressure on a given day was taken as the mean of three consecutive measurements.

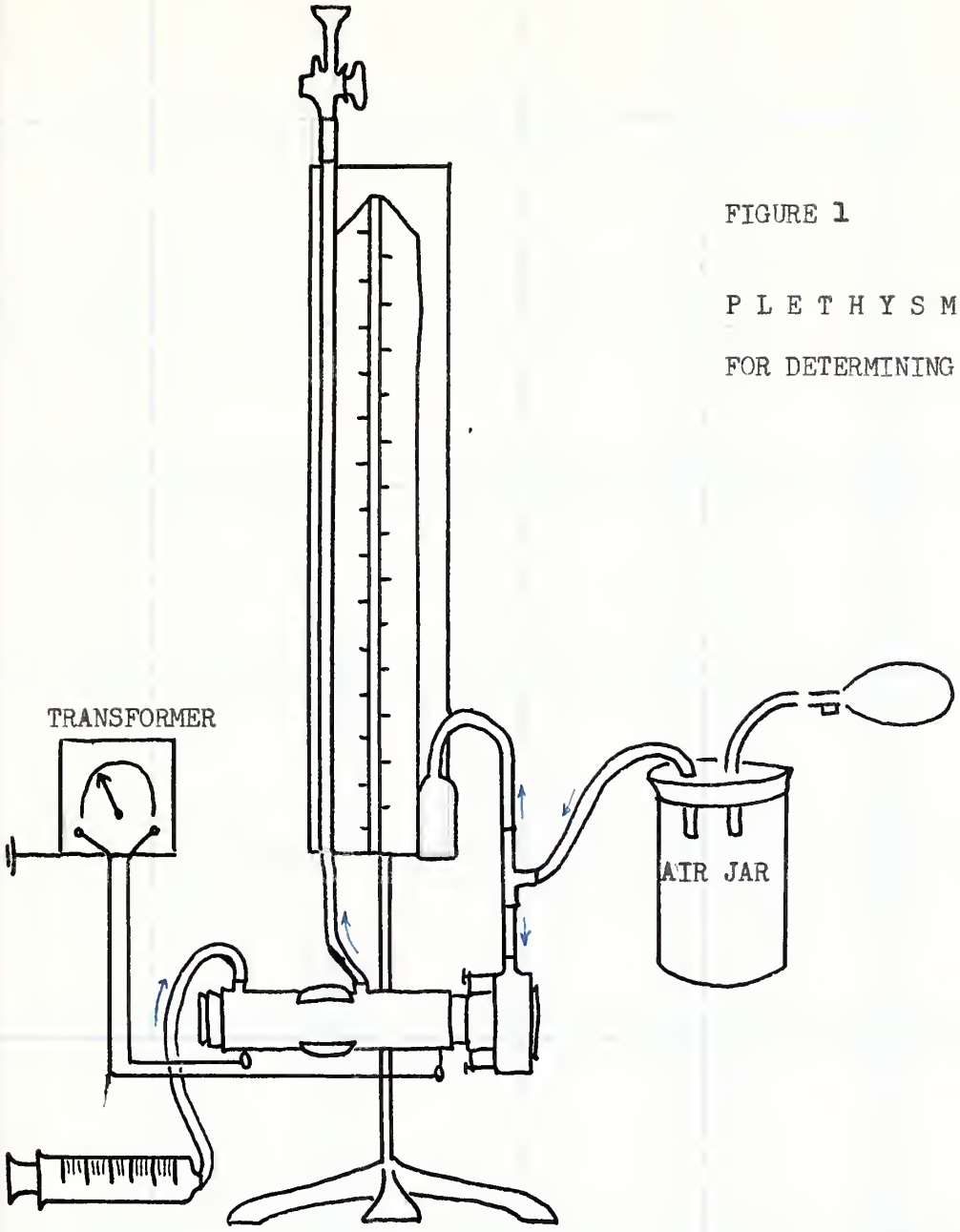
Figure-of-eight ligature of the left kidney was performed according to the technique of Grollman (1944). Contralateral nephrectomy was usually done one week following. Left adrenalectomy was accomplished simultaneous with the ligature of the left kidney; and right adrenalectomy, with the right nephrectomy. In Experiment (6) left adrenalectomy followed 2 weeks after the ligature of the left kidney and 1 week after the nephrectomy and adrenalectomy. After each operation and on the following day prophylactic doses of penicillin were given.

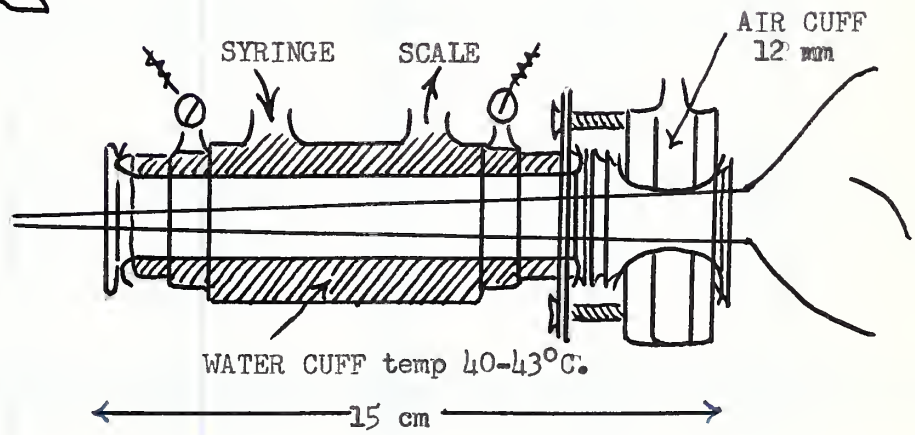
Radio-thyroidectomy was accomplished by the intraperitoneal injection of 1 mC I^{131} at least 10 weeks prior to the beginning of a given experiment. This dose is sufficient to produce a complete destruction of the thyroid gland with sclerosis in 30 days (Goldberg et al, 1950).

FIGURE 1

P L E T H Y S M O G R A P H

FOR DETERMINING BLOOD PRESSURE





The sodium salt of thyroxine was dissolved in alkali and demineralized water and frozen in aliquots sufficient for daily 0.2 ml. s.q. injection for each experiment.

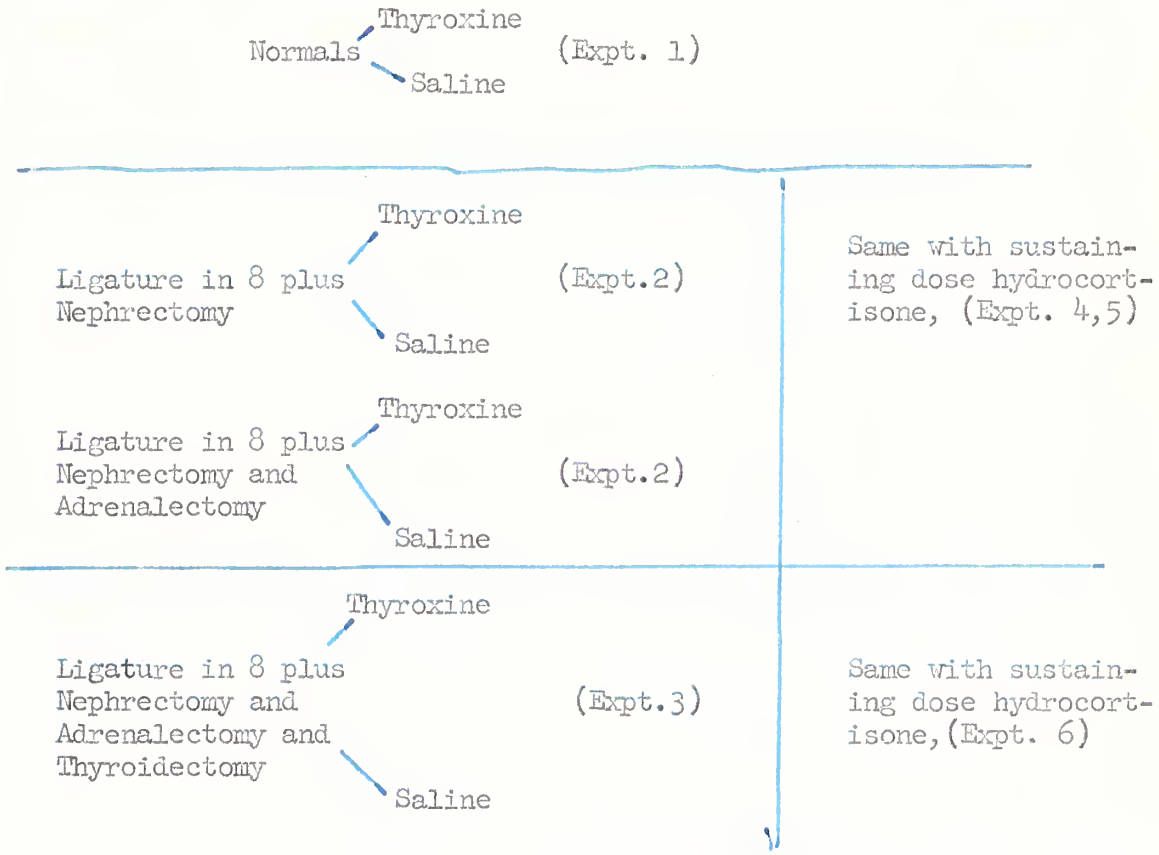
Hydrocortisone was weighed out in daily aliquots and, on the day of use, dissolved in methyl alcohol and water for 0.2 ml. s.q. injections. Hydrocortisone had been shown (Friedman et al, 1952, 1953) to have a smaller hypertensive effect than DOCA, and also not to be potentiated by 1% saline to drink and unilateral nephrectomy.

Upon death, the animals were examined grossly for kidney abscess, lung lesions, periarteritis and thyroid remanents.

At termination of each experiment, except experiment (3), autopsies were performed and the weight of the organs were determined within five minutes of sacrifice. The organs were carefully trimmed and gently blotted before weighing. Values were expressed as a percentage of body weight.

Representative tissues were taken from several experiments and submitted for microscopic inspection.

Summary of Experiments



EXPERIMENT 1

Preliminary experiments, using dose levels of 25 µg and 100 µg respectively, in animals with reduced renal mass (figure-of-eight ligature of one kidney and contralateral nephrectomy) given 1% saline to drink, had, in the first case (25 ug) shown little rise in blood pressure and, in the second case (100 ug) had resulted in the early death of most of the rats. Thyroxine at 50 ug (s.q. over 7 day or longer periods) given to experimentally prepared animals resulted in a satisfactory rise in blood pressure and relatively low mortality rate.

In Experiment 1, the effect of thyroxine at 50 ug dosage on normal animals was tested. Earlier investigators (Bachtold, 1950 and Krieger, 1956) had shown that thyroxine at 100-150 µg/day for more than two weeks and thyroxine at 117 ug/day for 21 days in normal animals caused a non-sustained rise in blood pressure. Did the 50 ug dose of thyroxine in experimentally prepared animals merely increase an effect which might be shown in normal animals?

Eight male rats of the Institute strain weighing between 103 and 151 grams were placed 2 per cage and given 1% saline and regular diet ad lib. For 7 out of the following 10 days, normal or basal blood pressure determinations were made. On day 10, 5 of the rats were begun on thyroxine, 50 µg on 0.2 cc s.q. and the remaining 3 rats on 0.085% saline. Injections were carried out for 8 days and blood pressure was determined on days 11, 14, 16 and 17. On the day following the last injection (day 9) after the blood pressures were read, 3 animals of the thyroxine treated group and 3 from the saline

control group were sacrificed and kidney and heart weights determined.

Body weights were measured at the beginning of the experiment, on the first day of injections, and at autopsy. Blood pressure determinations (Fig.2) are represented as averages of 2 days or 6 reading i.e. three individual readings per day x 2.

RESULTS:

TABLE 1: NORMALS (EFFECT OF 8 DAYS OF THYROXINE TREATMENT AT 50 ug

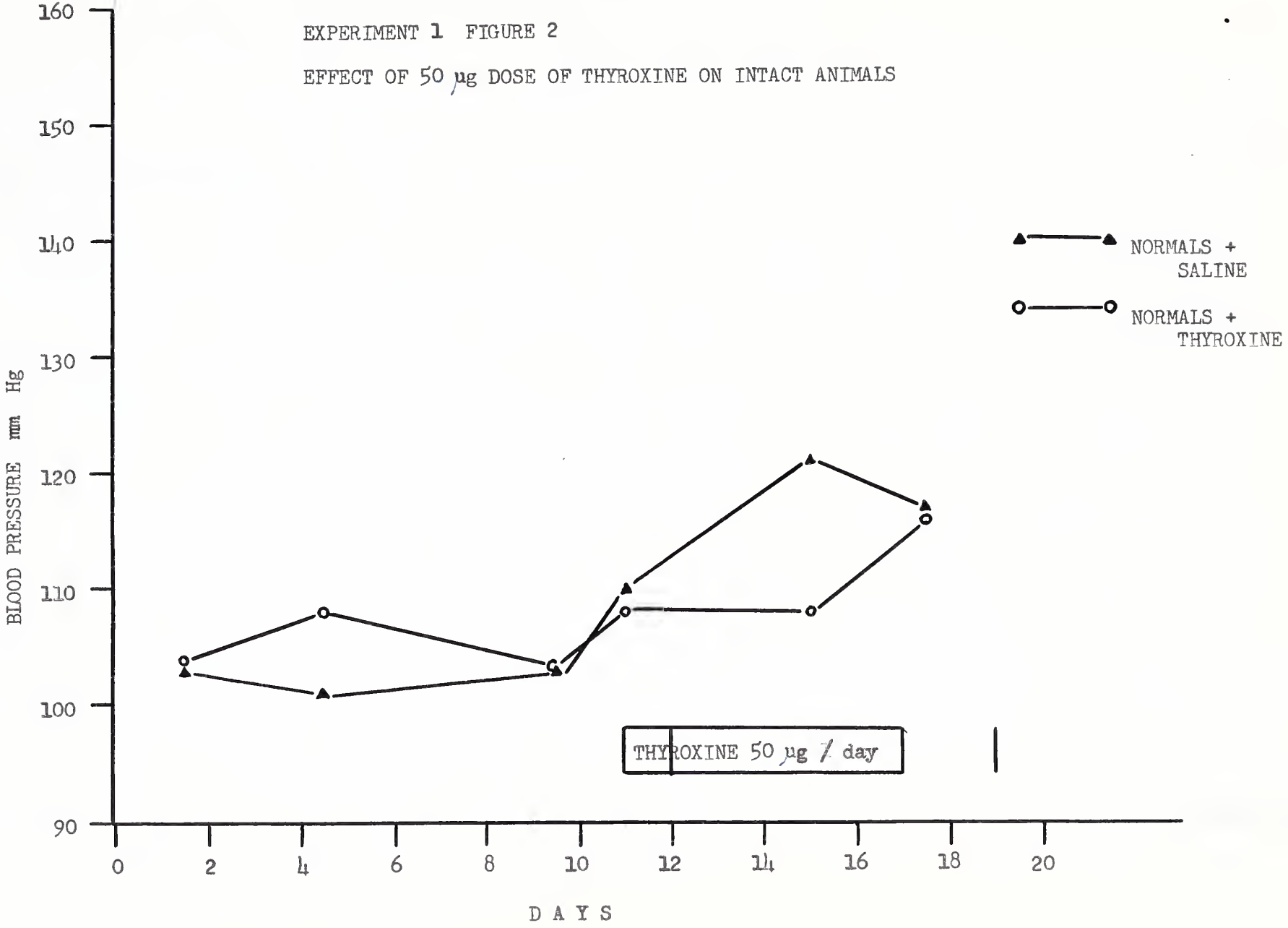
	Kidney (mg% BW+ SD)	Heart (mg% BW + SD)	Body Weight (% change)
Saline Control	.523 ± .014	.448 ± .011	+9.15 ± 0.21
Thyroxine	.554 ± .027	.446 ± .042	+2.19 ± 7.65
	$p > .6$	$p > .1$	$p > .3$

There were no significant differences in blood pressures, weight change or kidney and heart weight between the thyroxine and the saline treated group.

Although the small number of animals precludes a strong statement, it appears the 50 µg dose of thyroxine over an 8 day period does not result in a significant change in the blood pressure of normal animals, nor in heart or kidney weight.

EXPERIMENT 1 FIGURE 2

EFFECT OF 50 µg DOSE OF THYROXINE ON INTACT ANIMALS



EXPERIMENT 2

In an earlier work (Braun-Menendez, 1953) it was shown that the treatment of normotensive rats with moderate renal reduction (i.e. figure-of-eight ligature of one kidney, 4 to 5 months prior to therapy) with thyroxine (40 µg x 7 days) provoked a definite and in some cases sustained rise in blood pressure. In 3 normotensive rats, which had undergone figure-of-eight ligature of one kidney and contralateral nephrectomy 4 - 5 months previously, treatment with thyroid powder (15-25 mg qd x 10-18) resulted in an increase in blood pressure.

Although in the above animals there was no increase in blood pressure following the operations 4 to 5 months prior, there remains the question of changes having occurred inthe period before the beginning of thyroxine treatment which might have effected the results obtained, e.g. changes in kidney weight. Many workers have shown that once hypertension and/or its underlying vessel pathology have become established the effects of thyroxine therapy are changed.

In the following experiment, an effort was made to determine 1) the effects of thyroid administration on prepared animals, i.e. figure-of-eight ligature of one kidney and contralateral nephrectomy, during the latent period prior to the appearance of hypertension and 2) the effects of adrenalectomy on the above treatment. The latter would possibly indicate whether the effects of thyroxine were directly upon kidney growth and function or indirect,i.e. mediated through the adrenals.

The dosage used (50 µg) gave no increase in blood pressure in normal animals (Experiment 1).

Materials and Methods

58 white male rats of the Institute strain between 108 and 206 grams

(all but 5 between 140 and 206 grams) were divided into 5 groups. Four groups had figure-of-eight ligature of the left kidney followed one week later by right nephrectomy. Two of the four groups were adrenalectomized. Unilateral adrenalectomy was performed with each operation on the respective kidney. The fifth group contained normal controls.

		Treatment	Number of Rats
Group I	Ligature Left Kidney, Right Nephrectomy	Saline controls	8
Group II	" " " " "	Thyroxine 50 ug	14
Group III	" " " " ", Adrenal-x	Saline controls	11
Group IV	" " " " " "	Thyroxine 50 ug	20
Group V	Normal Controls	Saline	5

The rats were placed 2 per cage and given the regular Institute diet, and 1% saline ad lib. The latter was measured as ml. consumed per 100 grams body weight. Injections were begun on the day following the last operation and lasted for 7 days. Autopsies were performed on the surviving animals four days after the final injections. Blood pressure was determined on the 2nd, 4th, 6th, 8th and 10th days after the injections were begun. Blood pressure for the normal saline controls were taken on days 4, 8 and 10.

RESULTS

Survival

Group I 8/8

Group II 11/14

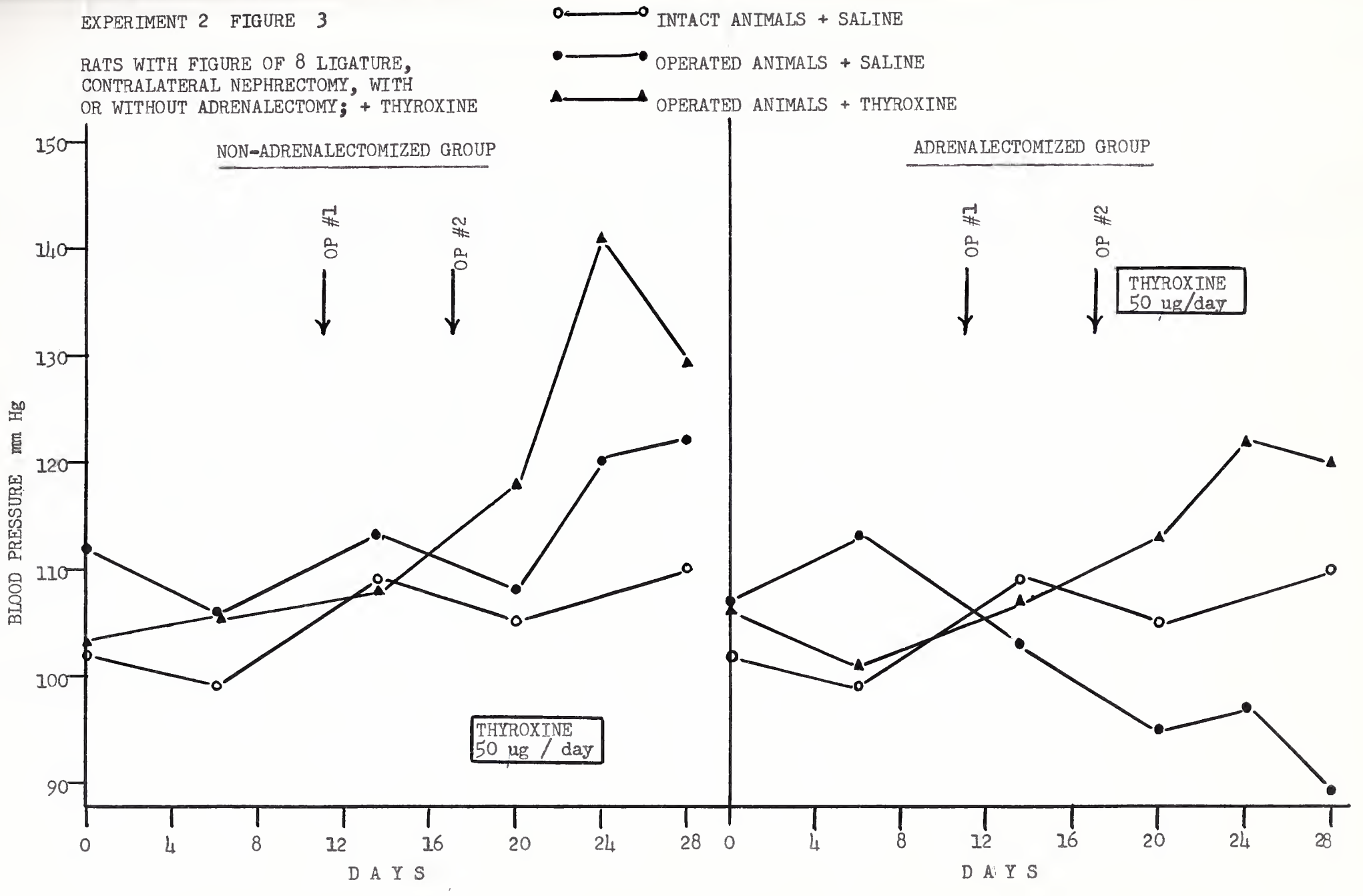
Group III 7/11

Group IV 6/20

Group V 5/5

EXPERIMENT 2 FIGURE 3

RATS WITH FIGURE OF 8 LIGATURE, CONTRALATERAL NEPHRECTOMY, WITH OR WITHOUT ADRENALECTOMY; + THYROXINE



Blood Pressure In both groups treated with thyroxine, the mean blood pressure was greater than the mean blood pressure of the saline groups. The significance of the blood pressure curves was determined by comparing three points in each group: day 2; the mean of days 4 and 6; and the mean of days 8 and 10. In comparing groups I and II, only the last point on the graph was significantly different (p less than .02 and .01) (Figure 3). In the nonadrenalectomized groups (I & II) or groups with reduced renal mass only, both the saline and thyroxine treated groups had higher mean blood pressures than the normal controls; however in the two points compared, only the thyroxine treated group was significantly different (p less than .01, less than .05).(Figure 4) In the adrenalectomized groups with reduced renal mass i.e. III and IV, the mean pressure of the normal rats fell between the saline and thyroxine treated groups but only the final point of the saline group was significantly lower. The thyroxine group mean blood pressure was not significantly higher. (Figure 4)

Water Consumption:

Water consumption between Group I and II was not significantly different. This also applied to Groups III and IV. However the mean of the saline consumption per 100 grams body weight of the two adrenalectomized groups, i.e. III and IV was lower than the group with reduced renal mass alone.

Autopsy: Table 2

Adrenals: The thyroxine treated group II was significantly higher than the normals (V), p less than .02. The saline group (I) was higher but not significantly so.

Kidneys: Both thyroxine treated groups II and IV were significantly heavier than their respective saline controls (Groups I and III) (p less than .02 and .05 respectively). When compared to the

EXPERIMENT 2 TABLE 2

Group	Weight % Change	Kidney mg%	Heart mg%	Adrenal mg%	Thyroid mg%
I RRM* + Saline	+9.30±6.6	.706±.050	.336±.038	.00210±.00045	.0085±.0012
II RRM + Thyroxine	+2.45±7.2	.867±.136	.403±.045	.00295±.00086	.0099±.0030
III RRM ± Adrenal-x + Saline	-1.7 ±5.0	.718±.082	.308±.018	.	.0099±.0021
IV RRM + Adrenal-x + Thyroxine	-13.33±6.1	.890±.124	.355±.056		.0086±.0018
V Intact Controls + Saline	+9.1±2.2	.419±.044	.289±.014	.00168±.00026	.0110±.0020

* RRM = Reduced Renal Mass (Figure-of-eight ligature of one kidney and contralateral nephrectomy)

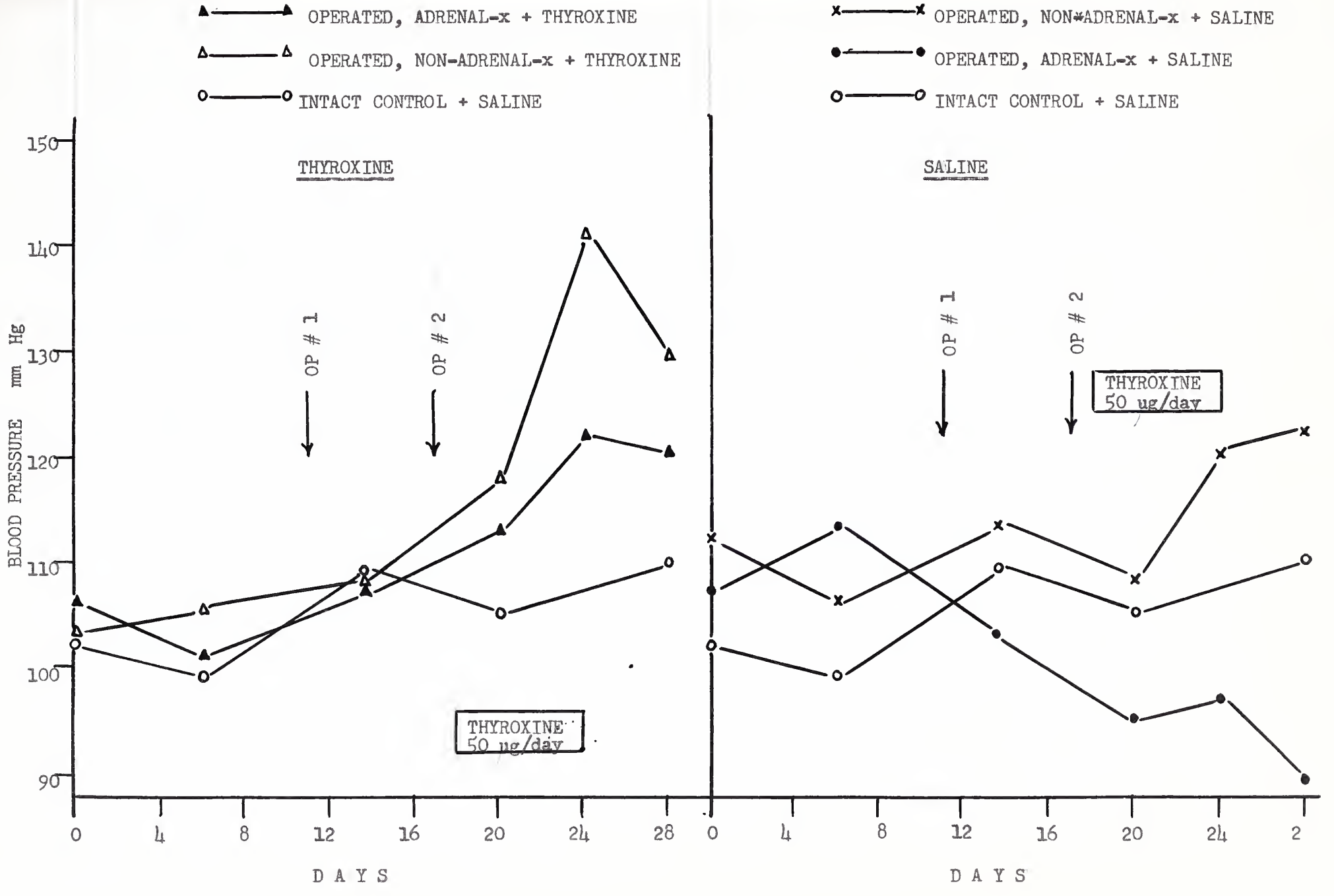
normal controls, all four groups were significantly different (p less than .01 in all cases). Within the saline treated groups (I and III) adrenalectomy caused no significant change. There was also no significant change in the thyroxine treated groups (II & IV)

THYROID: Adrenalectomized thyroxine treated group IV was significantly lighter than its respective saline control(III) $p < .01$, but the non-adrenalectomized thyroxine treated Group II was significantly heavier than its saline control I, $p < .01$. All groups with the exception of non-adrenalectomized thyroxine treated Group II were significantly lighter than the normal controls. The saline treated groups I and II and the thyroxine treated groups II and IV were not significantly different within their groups.

HEART: Of the thyroxine treated groups only that with reduced renal mass without adrenalectomy (II) was significantly higher than its operated control ($p < .05$). When compared to the normal saline controls, all groups with the exception of Group III (reduced renal mass with adrenalectomy plus saline treatment) were significantly different. The saline groups and the thyroxine groups were not significantly different among themselves.

WEIGHT: Both adrenalectomized groups lost weight and both non-adrenalectomized groups gained weight. Both thyroxine treated groups weighed less than their saline controls. With the slight exception of the saline treated non-adrenal-x animals, I, the other groups weighed less than the normal saline controls.

Experiment II demonstrates that in both adrenalectomized and non adrenal-x animals with reduced renal mass (i.e. figure-of-eight ligature and contralateral nephrectomy) thyroxine at a dose ineffective in normal animals is capable of raising blood pressure. Adrenalectomy, however, decreased the extent of the rise.



EXPERIMENT 2 FIGURE 4

Whereas thyroid treatment in both adrenalectomized and non-adrenalectomized rats caused increases in kidney weight both above respective saline and normal controls, there was no significant difference between the two thyroxine treated groups: this was also true for the saline controls. Only the hearts of the non-adrenalectomized thyroxine treated group were significantly increased above their saline controls. The adrenalectomized thyroxine treated rats and their saline controls showed no significant difference. There was no significant difference between the two thyroxine treated groups; this also held true for the saline treated groups.

Thyroxine treatment significantly decreased the weight of the thyroids (below their saline controls) in the adrenalectomized group; but in the non-adrenalectomized group, the thyroxine treatment increased thyroid weight above their saline controls. There was again no difference between the respective thyroxine treated groups; nor between the respective saline groups.

Thyroxine increased the weight of the adrenals significantly over the normals but not over the saline controls. Within the adrenalectomized and non-adrenalectomized groups treated with thyroxine, although no significant differences existed, the kidney responded less in the non-adrenalectomized group and the heart less in the adrenalectomized group. Adrenalectomized animals, both thyroxine and saline treated, consumed less saline; however within both saline and thyroxine treated groups of the adrenalectomized and non-adrenalectomized subdivisions there were no significant differences.

Further experiments will be necessary to assess the autopsy findings; however it seems that thyroxine is capable of reacting without the adrenals to raise blood pressure.

EXPERIMENT 3

This experiment repeats the preceding experiment (2) but employs thyroidectomized as well as adrenalectomized animals to eliminate possible influences of endogenous thyroid secretion. In the preceding experiment the thyroid glands in non-adrenalectomized animals with reduced renal mass were significantly increased over the saline controls with reduced renal mass following seven days of thyroxine treatment.

Materials and Methods: Twenty-two white male rats of the Institute strain, weighing between 146 and 201 grams, except for two weighing 127 and 216, were thyroidectomized with intraperintoneal injection of 1 mC I^{131}, seven weeks prior to the beginning of the experiment for the thyroxine group and 10 weeks prior to the onset for the saline group. The thyroxine treated group consisted of 10 animals. Figure-of-eight ligature of the right kidney and right adrenalectomy was followed nine days later by nephrectomy and left adrenalectomy. Injections of 50 µg/day thyroxine were begun on the day following the last operation and continued for seven days. The experiment was terminated two days after the final injections(nine days after the beginning of the experiment). The saline group consisted of 12 animals with the above operations and lasted the same time. Blood pressures were determined almost daily, except for day three in the thyroxine group and day four in the saline group. Autopsies were not performed and the animals were allowed to continue with periodic blood pressure determinations until death.

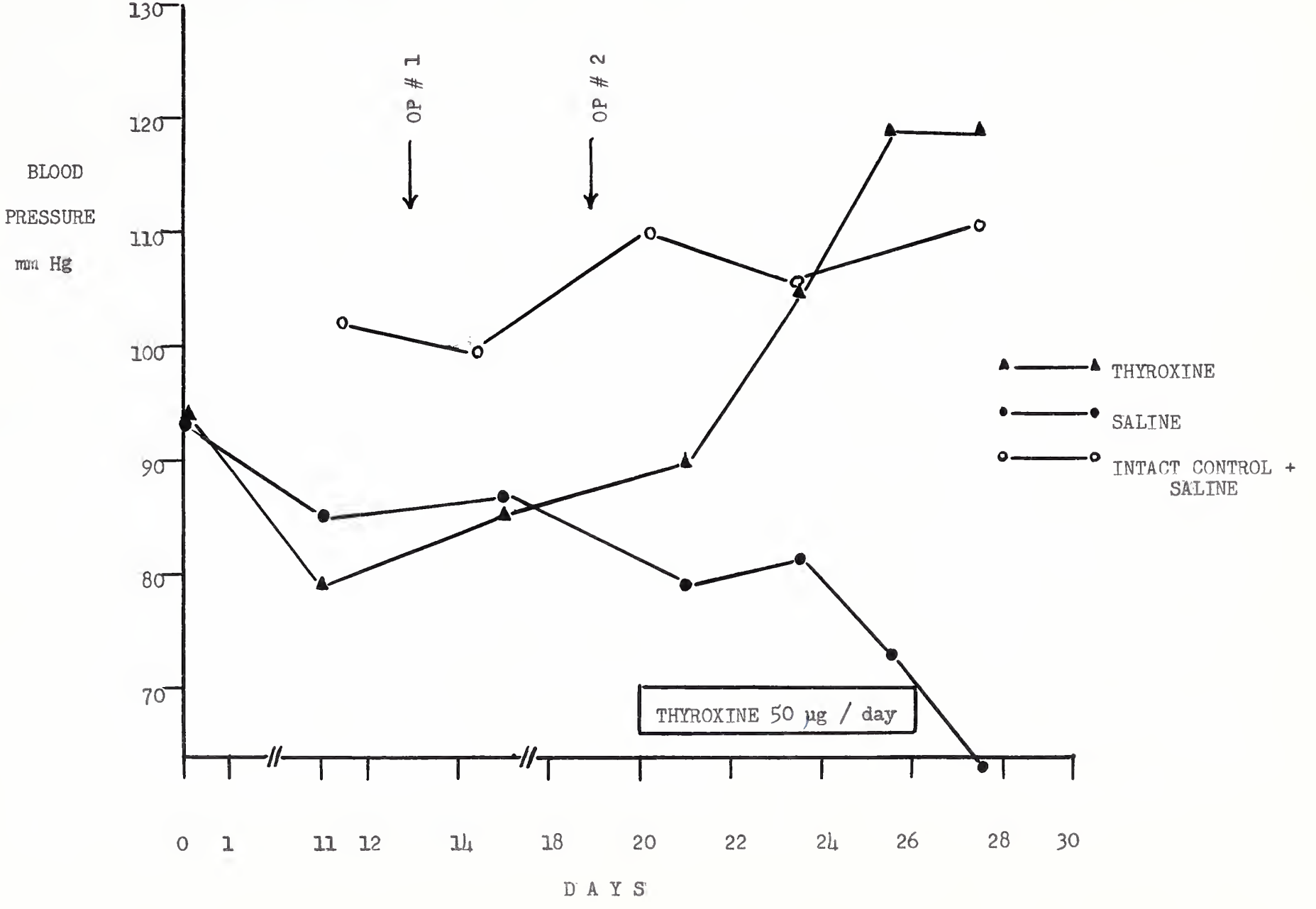
Results: Survival (to ninth day)

Thyroxine Group 5/10 (1 animal survived 14 days after adrenalectomy)

Saline Gruup 6/12 (1 animal survived 14 days after adrenalectomy)

EXPERIMENT 3 FIGURE 5

ADRENALECTOMIZED, THYROIDECTOMIZED RATS WITH FIGURE OF 8 LIGATURE OF ONE KIDNEY AND CONTRALATERAL NEPHRECTOMY TREATED WITH THYROXINE



Blood Pressure: (Figure 5) The thyroxine group blood pressure increased above its base during treatment and the saline group decreased below its pre-experimental levels during treatment. The curves (Figure 5) represent average of two days readings. The last two points on the graph are significantly different (p less than .01) and the third from the end, not significant at p greater than .05.

Weight Change: Weights declined but were not significantly different. The thyroxine treated group lost 12.1± 13.8 per cent and the saline group lost 13.7 ± 15.0 per cent.

It appears in this experiment that thyroxine maintained but did not increase significantly the blood pressure of both thyroidectomized and adrenalectomized rats with reduced renal mass.

The mortality in both Experiments 2 and 3 reflects the delicate state of the animals. For this reason, a sustaining dose of hydrocortisone was added and both experiments were repeated as follows.

EXPERIMENT 4

This experiment repeats Experiment 2 using sustaining doses of hydrocortisone to attempt to improve survival rates and to bring the animals to a better state of physiologic balance than they were without any endogenous steroid. Friedman et al (1952, 1953) had demonstrated that hydrocortisone in uninephrectomized rats at .05 mg did not cause steroid hypertension nor was its action potentiated by 1% saline as drinking water.

Materials and Methods

Twenty-four white male rats of the Institute strain weighing between 127 and 188 grams were divided into two groups. In one, ligature of the left kidney and left adrenalectomy was followed one week later by right nephrectomy and adrenalectomy. The other group was operated upon at the same time but adrenalectomies were not performed. All rats were given 0.25 mg hydrocortisone on the day of the second operation and 0.5 mg thereafter. Both groups were subdivided into saline controls and thyroxine treated animals. The thyroxine groups received 50 µg thyroxine daily beginning the day after the last operation and lasting for fourteen days. The hydrocortisone was continued for two days beyond and the survivors were sacrificed on the next day or seventeen days after adrenalectomy.

Blood pressures were determined on days 3,4,5,7,9,11,14 and 16 after the second operation. The animals were given 1% saline ad lib.

Results:

Survival (After Seventeen Days)

Group I - Reduced Renal Mass, Adrenalectomy - Saline 5/8

Group II - Reduced Renal Mass, Adrenalectomy - Thyroxine 4/9

Group III- Reduced Renal Mass - Saline 2/3

Group IV - Reduced Renal Mass - Thyroxine 4/4

Blood Pressure: In the non-adrenalectomized group there was no difference between the thyroxine group and saline controls. In the adrenalectomized group, the mean thyroxine blood pressure was higher than the saline control, only the last point on the curve showed a significant difference ($p < .05$) - however blood pressures of both groups fell during the course of the experiment.

Autopsy: (Table 3)

Kidney: In both adrenalectomized and nonadrenalectomized groups, thyroxine treated kidneys were heavier than their saline controls, but only significantly so ($p < .01$) in the adrenalectomized group. The body weight of the nonadrenalectomized thyroxine treated group was significantly heavier than the saline injected adrenalectomized group ($p < .02$) .

Heart: The saline treated adrenalectomized group I was significantly lighter than all other groups.

Thyroid: The mean thyroid weights in the thyroxine treated Groups II and IV were lower than their respective saline controls, but not significantly so. There was also no significant difference between the thyroxine treated groups themselves (II vs. IV) or the saline controls (I vs. III).

Adrenals: The thyroxine treated group mean adrenal weight was higher than the saline controls but not significantly so. ($p > .3$)

EXPERIMENT 4 TABLE 3

Group and No.	Weight % Change	Kidney mg %	Heart mg %	Adrenal mg %	Thyroid mg %
I RRM*, adrenal-x + Saline (5)	+2.85±7.1	.740±.062	.332±.052		.0138±.0022
II RRM, adrenal-x + Thyroxine (4)	+1.4±11.8	.881±.033	.444±.063		.0119±.0019
III RRM + Saline (2)	+0.13±12.24	.778±.103	.454±.015	.00218±.00022	.0131±.0015
IV RRM + Thyroxine (4)	+2.36±14.5	.849±.057	.449±.078	.00252±.00038	.0127±.0030

* RRM = Reduced Renal Mass (Figure-of-eight ligature of one kidney and contralateral nephrectomy)

Weight: All groups gained weight but exhibited no significant differences when compared.

The poor results obtained in Experiment IV as opposed to Experiment II with regard to blood pressures correlate with the poor differences exhibited by the kidney and other organs at autopsy. This experiment is repeated in Experiment V using a different strain of animals and extending the experiment over a longer period of time.

EXPERIMENT 5

Earlier work by Lascano-Gonzalez (1934) on rats of the Institute strain had demonstrated the appearance of accessory adrenal glands in those rats which survived bilateral adrenalectomy. The maximum adrenal insufficiency occurred five to fifteen days post-operatively. It was with the intent of avoiding adrenal secretions from the accessory glands that all experiments reported - except this one which was carried out on a different strain - were never carried beyond two to three weeks. However, it was reported that the Wistar rats of the Argentine Atomic Energy Commission strain did not exhibit any significant accessory adrenal growth post adrenalectomy. This allowed the carrying out of a more prolonged experiment with adrenalectomized rats on sustaining doses of hydrocortisone which would repeat with a greater chance of success the previous experiment (4).

Materials and Methods:

Eighteen male Wistar rats weighing between 147 and 167 grams were divided into two groups. Group I consisted of eight operated saline controls and Group II, of 10 operated thyroxine treated experimentals. Ligature of the left kidney and simultaneous left adrenalectomy was followed one week later by combined right adrenalectomy and nephrectomy. On the day prior to the second operations, Groups I and II were begun on 0.5 mg hydrocortisone s.q.; this dose was continued until the twelfth day after the second operation whenit was decreased to 0.25 mg, this later dose continuing daily until the end of the experiment. On Day One following the second operation, Group II was begun on 10 µg thyroxine s.q.; on Day Thirteen, this was increased to 25 µg; and on Day Twenty-five, this was again increased to 50 µg, this last dose continuing for eight days until the end of the experiment. The hydrocortisone at 0.25 mg was continued for two days beyond the termination of thyroxine therapy. On the Thirty-fourth day after the second operation, the animals were sacrificed.

All animals were kept in individual cages and given ad lib food and 1% saline. The blood pressures of Groups I and II were measured every second day. Autopsies were performed in the usual manner using the Roller-Smith Balance. Four normal untreated animals with pressure in the normal range were also sacrificed.

Results:

Survival: All animals, except one in the Saline treated Group I, survived.

Blood Pressure: (Figure 6) Determinations are represented as the average of the mean o f two successive days' readings. Approximately midway in the course of the treatment with the dose level of 10 µg thyroxine, the thyroxine Group II had a higher mean blood pressure than the Saline control. This difference was maintained until the end of the experiment; however, only the last two points on the graph were significantly different ($p < .01$ and $p < .05$).

Weights: Both Groups I and II gained weight. Group I, +50.1±6.1 per cent and Group II, 37.8±2.4 per cent. This represented a statistically significant difference of $p < .05$ in favor of the saline controls.

Autopsy:

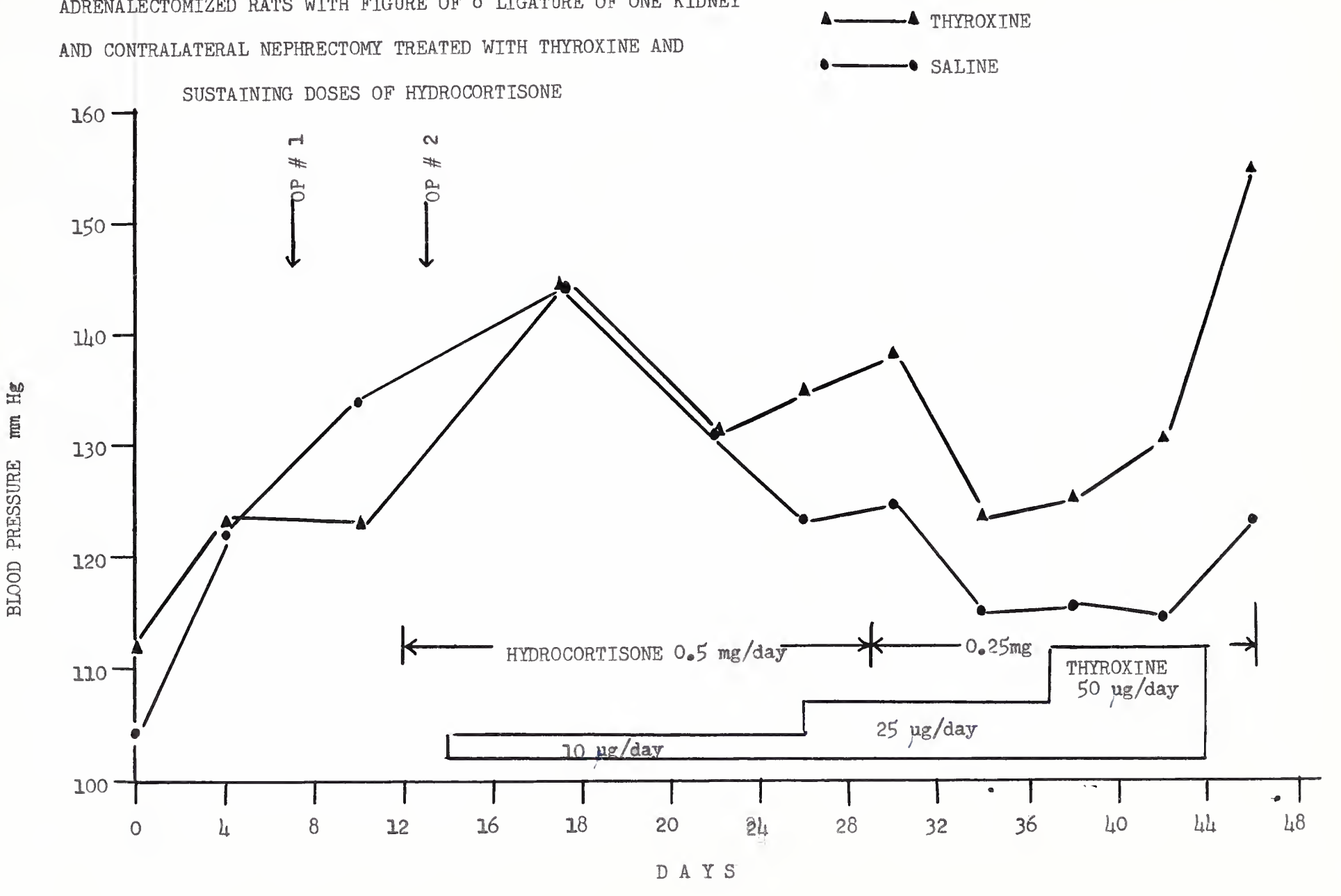
Kidneys: Both operated Groups I and II were significantly ($p < .01$) heavier than the normals; and the thyroxine treated Group II was significantly heavier ($p < .01$) than its saline control Group I.

Heart: The thyroxine treated Group II was significantly heavier than both its saline control Group I ($p < .01$) and the normal controls. ($p < .01$) The saline control Group I, however, was not significantly heavier than the normal controls ($p < .05$).

Thyroid: The only significant difference existed between the thyroxine treated Group II which was lighter ($p < .01$) than the normal control.

EXPERIMENT 5 FIGURE 6

ADRENALECTOMIZED RATS WITH FIGURE OF 8 LIGATURE OF ONE KIDNEY AND CONTRALATERAL NEPHRECTOMY TREATED WITH THYROXINE AND SUSTAINING DOSES OF HYDROCORTISONE



EXPERIMENT 5 TABLE 4

Group and No.	Weight % Change	Kidney mg%	Heart mg%	Thyroid mg%
Intact Controls (4)	---	.414±.005	.3025±.014	.0120±.0004
RRM, Adrenal-x Saline (7)	+50.1±6.1	.685±.024	.348±.016	.0106±.0008
RRM*, Adrenal-x Thyroxine (10)	+37.8±2.4	.820±.018	.413±.031	.0083±.0004

*RRM (Reduced Renal Mass = Figure-of-eight ligature of one kidney and contralateral nephrectomy)

Experiment 5 again exhibits the ability of thyroxine to increase blood pressure in adrenalectomized rats with reduced renal mass. With sustaining doses of hydrocortisone, the saline group maintained an almost normal blood pressure level. This gives more significance to the rise in blood pressure of the thyroxine treated group.

EXPERIMENT 6

This experiment repeats the earlier Experiment (3) using sustaining doses of hydrocortisone in thyroidectomized and adrenalectomized rats with reduced renal mass.

Materials and Methods

Ten white male rats of the Institute strain, weighing between 136 and 165 grams, which had been given 1 mC I^{131} nine weeks prior to the onset of the experiment were subjected to the following operations: 1) Figure-of-eight ligature of the left kidney, followed seven to,nine days later by 2) Right Adrenalectomy and Right Nephrectomy, followed four to six days later by 3) Left Adrenalectomy.

The animals were divided into two groups: Group I: Five animals received hydrocortisone and saline, and Group II: Five animals received thyroxine and hydrocortisone. One mg hydrocortisone was given on the day of the last operation in divided doses and a sustaining 0.5 mg divided daily dose thereafter. Saline and thyroxine (50 µg) injections were begun on the day following the last operation and continued for twelve days. The hydrocortisone was continued two days beyond that.

Animals were kept in separate cages and given normal chow and 1% saline to drink. Autopsies were performed on the day following the last hydrocortisone injection or sixteen days after complete adrenalectomy. Blood pressures were determined each second day after the last operation. Kidneys and hearts were weighed and the thyroid region inspected grossly.

Results

Survival:

Group I: RRM, Adrenal-x, Thyroid-x + Saline	3 / 5
Group II: RRM, Adrenal-x, Thyroid-x + Thyroxine	4/ 5

EXPERIMENT 6 TABLE 5 Adrenalectomized, Thyroidectomized Rats with Reduced Renal Mass

Group and No.	Weight %Change	Kidney mg%	Heart mg%
Group I - Saline + Hydrocort.(4)	-3.3±8.4	.611±.033	.371±.041
Group II Thyroxine + Hydrocort.(3)	-4.4±1.8	.739±.084	.393±.027

Results (cont.)

All animals showed no evidence of thyroid tissue grossly.

Blood Pressure: (Figure 7) The thyroxine treated group showed an increase in blood pressure over the saline treated group. The last two points on the graph were significantly different, $p < .05$ and $p < .01$, respectively.

Body Weight: Both groups lost weight. Group II (Thyroxine) -4.4±1.8 per cent and Group I)(Saline) -3.3±8.4. These differences were not significant.

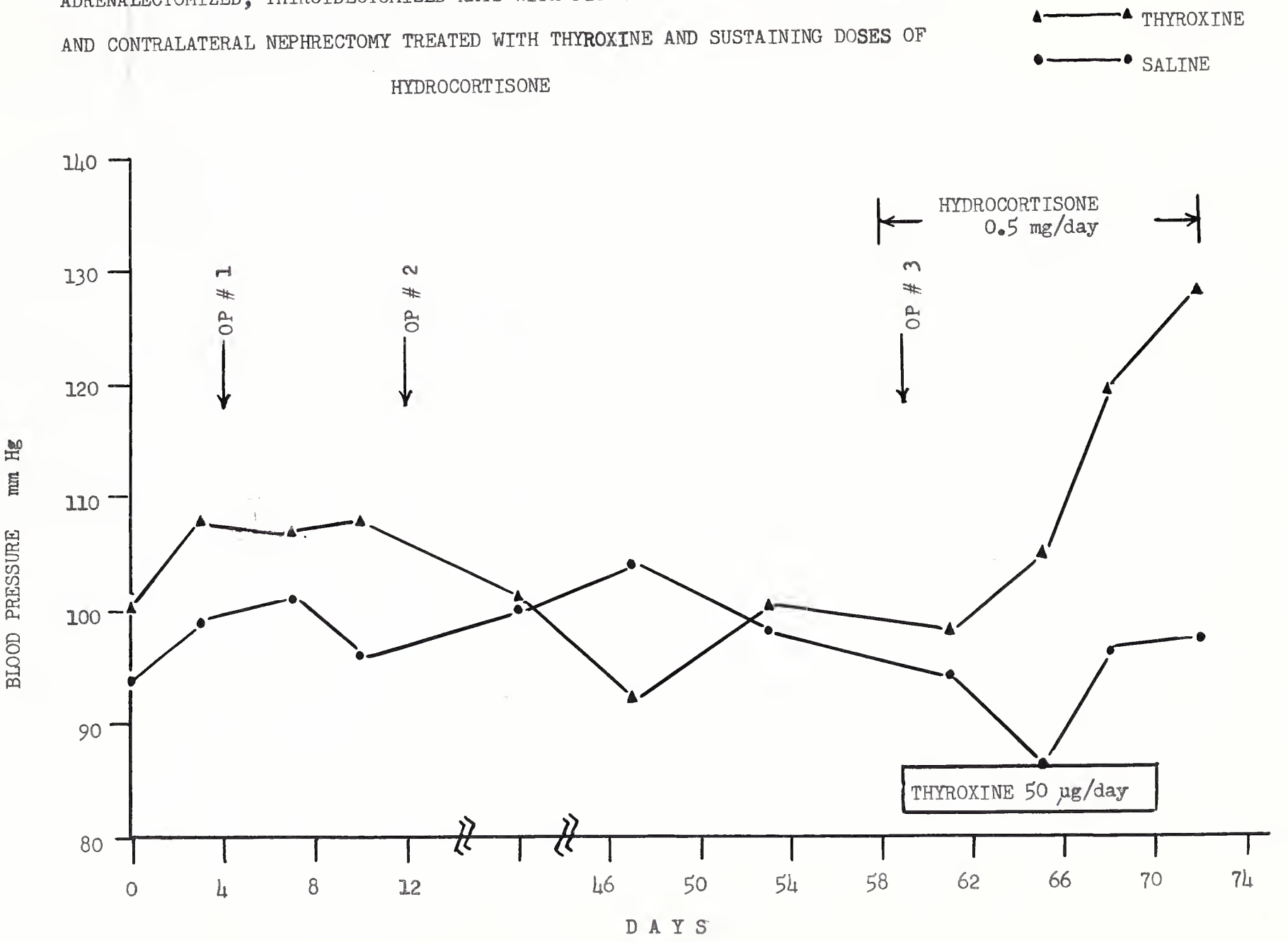
Autopsy: The Kidneys in the thyroxine treated group were significantly heavier ($p < .05$) than the saline group. The Hearts in the thyroxine treated group were also heavier than the saline treated group but not significantly so.

It has again been demonstrated that thyroxine can increase above normal the blood pressure of adrenalectomized rats. This continues to correlate well with the increase in kidney weight and less well with the increase in heart weight.

A compilation of many determinations of blood pressure showed the distribution curve of thyroidectomized animals to be lower than that of normal animals. The curve for the normal animals gives good agreement

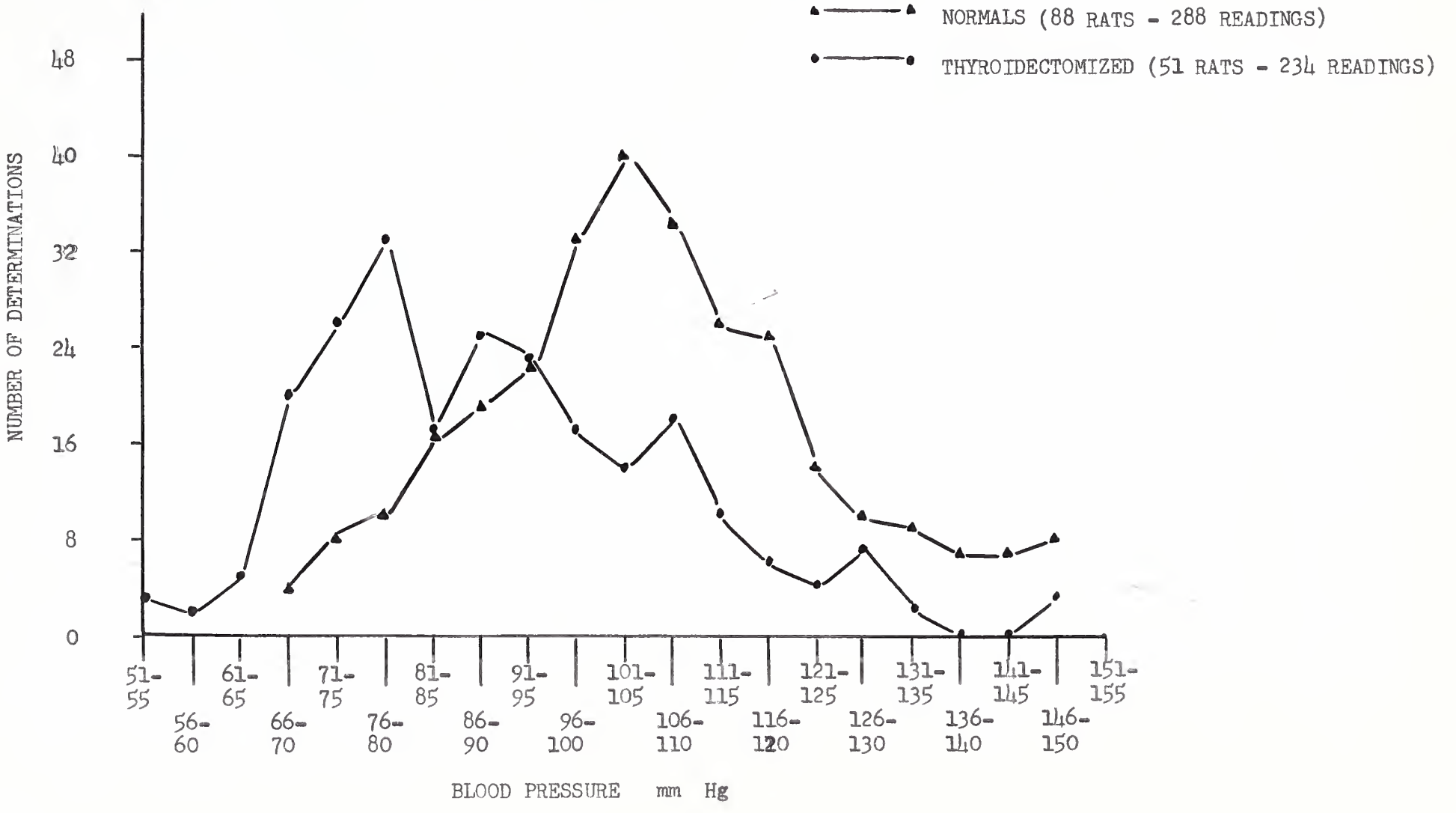
EXPERIMENT 6 FIGURE 7

ADRENALECTOMIZED, THYROIDECTOMIZED RATS WITH FIGURE OF 8 LIGATURE OF ONE KIDNEY AND CONTRALATERAL NEPHRECTOMY TREATED WITH THYROXINE AND SUSTAINING DOSES OF HYDROCORTISONE



with blood pressure obtained in normal rats by other authors. (Figure 8).

FIGURE 8 EFFECT OF THYROIDECTOMY ON BLOOD PRESSURE OF RATS



RESULTS:

It has been demonstrated that thyroxine treated rats with figure-of-eight ligature of one kidney and unilateral nephrectomy, which have been adrenalectomised or both adrenalectomized and thyroidectomized, show a restoration of blood pressure to above normal or slightly hypertensive levels. This occurred at a dose level ineffective in normal animals. This also occurred during the lag phase prior to the time of the usual appearance of experimental renal hypertension. The effect on blood pressure of thyroxine was augmented by supplying sustaining doses of hydrocortisone. In experiment 5, the longer term effects of thyroxine administration were amply demonstrated. These results were enhanced when compared to the saline controls because of the decrease, quite large in several instances, of blood pressure below normal levels.

Treatment of adrenalectomized rats with thyroxine increased the mortality, as had previously been shown (Zwemer, 1927; Hoffman et al, 1948). This was also true of adrenalectomized-thyroidectomized rats treated with thyroxine. Sustaining doses of hydrocortisone given to such animals, however, decreased the large mortality, confirming Koelsche and Kendall (1935).

In Experiments 2 and 4, adrenalectomy did not cause any significant difference in the effects produced by thyroxine on kidney, heart and thyroid weight. With the exception of Experiment 4, thyroxine caused a significant increase in kidney weight over both saline and normal controls in the adrenalectomized and also in the nonadrenalectomized groups. This was well correlated with the effect on blood pressure. The effect of thyroxine on heart weight was less striking (Tables 4&5). The weight of the adrenal glands was increased (Experiments 2 and 4),

but the difference was not significantly greater than the saline controls. This is in agreement with Pekkarinen et al, 1951; Preston 1928; and Ingle and Higgins, 1938.

Except for the adrenalectomized rats in Experiments 2 and 4, thyroxine caused the non-adrenalectomized rats to gain less weight than their saline controls; and all adrenalectomized thyroxine treated rats to lose more weight than their saline controls.

As for 1% saline drinking water, thyroxine made no significant difference between saline or thyroxine treated groups, whether these animals were adrenalectomized or not.

Microscopic examination of tissues taken from autopsied animals failed to show any significant histopathological difference between experimental animals and controls.

DISCUSSION:

That thyroxine has a hypertensive effect on animals with reduced renal mass has been confirmed. That thyroxine has a definite if not marked effect on adrenalectomized animals with reduced renal mass has also been demonstrated. The effect on blood pressure in the absence of adrenals is quantitively less; however, the renotrophic effect is statistically undiminished. Accepting the role of the kidney in experimental renal hypertension, one finds that the adrenals are qualitatively unnecessary for renal hypertrophy; and hence their effect on increased blood pressure is quantitative or "permissive".

If the adrenal's role is minimized, it is interesting to investigate other possible factors in the mechanism of thyroid action.

Brewster (1954) and Page and McCubbin (1952) showed a correlation between thyroid activity and the sensitivity of the heart and blood vessels of dogs to infusions of catecholamines. The same was demonstrated in rats by Osorio (1956). The effect of such changes in vascular reactivity or increased secretion of catecholamines seems of minor rather than major importance here. In Experiment 1, a 50 µg dose of thyroxine given to normal animals had no measureable effect on blood pressure. In Experiment 5 which lasted over a month, it would be hard to concede a major role to a continuing change in vascular reactivity (without histologic change) or increased secretion of catecholamines, especially in adrenalectomized animals. Other investigators (Alpert, 1937, Pickering, 1955, Von Euler, 1956) have found no change in levels of catecholamines in experimental renal hypertension.

Thyroxine's effect in increasing heart weight is well known. Sandler and Wilson (1959) studying the production of cardiac hypertrophy by thyroxine in the rat found that increased heart weight was due to muscle hypertrophy and not to changes in water or electrolytes. The response of the heart was secondary to an increased metabolic rate and

and hence demand for oxygen (Rasmussen, 1941). Krieger(1956) found that dinitrophenol increased oxygen consumption; however, it was only thyroxine that increased blood pressure.

Fregly and Gonzales (1961) found that oxygen consumption in renal hypertensive rats did not have a close relationship to systolic blood pressure. These authors asked whether the thyroid weight ratio increased in response to a rising systolic blood pressure or to an increasing heart weight ratio. In our experiments, studying the lag period before the appearance of hypertension, the thyroxine injections were effective in the absence of both prior increase in blood pressure and cardiomegaly.

There is no doubt that adrenalectomy decreased the vitality of our experimental animals, and hence lessened the effect of thyroxine or rather increased mortality to these injections. Sustaining doses of hydrocortisone, however, improved the experimental conditions and hence the ability of thyroxine to enhance renal hypertension in the absence of adrenal glands.

Further study of the role of the thyroid in experimental renal hypertension are indicated. Over a period one might study I^{131} uptake; the changes in content of thyroid hormones in the gland and plasma; the histology of the thyroid during the course of development of renal hypertension; and respiration in various organs and tissues during the phases of hypertension, thyroid hyperfunction and adrenal insufficiency.

Very little is known about the early stages in experimental renal hypertension. As in humans, once hypertension becomes established the factors that may have given rise to it diminish in importance. Green et al

(1952) demonstrated the un-importance of both the adrenal and the thyroid in post DCA hypertension. In humans, thyroidectomy (Kountz and Humpelmann, 1940) and antithyroid drugs (Beamish and Adamson, 1945) failed to lessen established hypertension. The future seems to lie more clearly with the prevention rather than the treatment of the disease. And it is to that end that studies of the many factors giving rise to hypertension are important.

RESUMEN

Ha sido demostrado que en ratas con ligadura en ocho de un riñon y nefrectomia contralateral y que han sido adrenalectomizadas o adrenal-ectomizadas y tiroidectomizadas; el tratamiento con tiroxina les determina un restablecimiento de la presion arterial, en niveles por encima de lo normal o discretamente hipertensivos. Este efecto se observa durante la fase previa a la aparicion de hipertension con dosis que no producen modificaciones en animales normales. El efecto de la tiroxina sobre la presion arterial fue potenciado por la hidrocortisona en las dosis habituales de mantenimiento.

El tratamiento con tiroxina determino una mortalidad aumentada en las ratas adrenalectomizadas o adrenalectomizadas y tiroidectomizadas; las dosis de mantenimiento de hidrocortisona disminuyeron el grado de mortalidad.

El efecto de la tiroxina sobre el peso del riñon , del corazon y de la tiroides no fue modificado significativamente por la adrenalectomia.

El efecto de la tiroxina sobre la presion arterial tuvo una buena correlacion con el grado de hipertrofia renal conseguido con el tratamiento.

Han sido discutidos los posibles mecanismos de accion del efecto encontrado, presentandose tambien un resumen de la literatura sobre el papel de la tiroides en la hipertension renal experimental.

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