EFFECTS OF THYROXINE, SEX HORMONES, AND STRESS ON HORMONAL INTERACTIONS AS MEASURED BY GLAND AND ORGAN WEIGHTS, METABOLIC RATE, RESISTANCE TO EXHAUSTION, AND ADRENAL HISTOLOGY OF NEW HAMPSHIRE CHICKS

by

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INTRODUCTION

The organic substances which are called hormones effect chemical changes which constitute the "slow" control of the life-processes of living things. This function is in contrast with the "quick" control of the nervous system of animals, and the catalyzing action of vitamins and enzymes. Hormones are known to control such diverse processes as metabolic rate, salt metabolism, sugar metabolism, sexual development and reproduction, growth, lactation, calcium metabolism, and circulatory processes. Many other hormonal functions are suspected, and consequently much work of a basic nature is needed to bring these to light. This is particularly true in regard to the chick, for work on the endocrinology of this animal has often been limited to those factors directly affecting the quantitative characters such as egg production, rate of growth, and rate of feathering. The basic endocrine nature of the chick has been largely ignored, and therefore the relationships which must certainly exist between all the endocrine glands have not come to light in this animal as rapidly as they have in others. Further, the role of the endocrine system of the chick in the response to external stress is unknown, although this factor is being widely investigated in mammals. It is felt that an investigation of basic inter-glandular relationships in the chick, and their response to stress, may be of importance to the poultry producer as well as to the endocrinologist. A brief discussion of the nature of stress and the role of the endocrine system in it will serve to clarify this statement.

It has become increasingly apparent in recent years that unusually harsh environmental conditions exert profound influences on the body-processes of living things. Evidence has accumulated to the effect that many "chronic" diseases of the higher vertebrates have their origin

in long-continued external stresses. It is also accepted that stress may affect nutritional requirements, growth rate, reproductive activity, and resistance to disease, even when applied for a relatively short time. The stress phenomenon is therefore important to the practical animal breeder as well as to the scientist. Basic research on laboratory mammals has revealed new facts about their mechanisms of adjustment to the environment. The endocrine system has been shown to play a key role here, and consequently, new functions of some hormones have become known.

Although the endocrine system (particularly the adrenal cortex) is known to be important in adaptive responses to stress, little is known about the hormonal interrelationships which may be involved, beyond those existing between the anterior pituitary and the so-called target glands. If current theories are correct, increased activity on the part of the anterior pituitary to secrete one "trophic" hormone decreases the secretion of the others. For example, if the pituitary is induced to secrete large amounts of thyrotropic hormone (TSH) by the administration of a goiterogenic compound, it might be expected that the production of adrenocorticotrophic hormone (ACTH) would be decreased. A consequently decreased activity on the part of the adrenal cortex would then render the animal unable to withstand stress. This effect might be reinforced by the concurrent lack of thyroxine.

Evidence for the existence of such an "exclusive" mechanism is by no means conclusive. It is possible that the anterior pituitary may secrete ACTH at high levels simultaneously with increased TSH output. The present tests were designed to investigate the response to stress of growing chicks which received controlled levels of a thyroxine containing compound.

Another aspect of this hormonal control which is not accepted by all workers is pertinent to the problem. That is the belief that the secretions of the target glands (thyroid, adrenal, etc.) effect their control of pituitary secretions by acting upon the cells of the latter gland. If this is true, then an increased level of circulating thyroxine, for example, inhibits the power of the cells of the anterior pituitary to secrete TSH. A general revision of the pituitary activity may follow, causing an alteration in the secretion of other hormones, as expressed in the theory previously discussed. If, however, the control of the pituitary hormones is a deactivation phenomenon rather than a secretion-control phenomenon and occurs in the body fluids, apart from and independent of the pituitary itself, then alteration of the level of one trophic hormone should have no effect on the levels of the others. The view is held by some workers that this is the true mechanism of hormonal control, and there is experimental evidence to support it.

The present tests were performed to investigate the response of the physiology of the chick to altered endocrine activity. Emphasis was placed on interglandular relationships as evidenced by changes in body weight, and weights of the endocrine glands, heart, and comb, as well as changes in metabolic rate and adrenal histology. Fundamental information was sought on the response of the chick to stress, and on the relationship between glandular size and activity.

Interaction Phenomena.

A. Pituitary-target glands. The role of the anterior pituitary in the control of the activity of other endocrine glands is too well known to bear extensive discussion here. Several excellent treatments of the subjects are available (30, 81, 89). However, the method by which this control is accomplished, though it may sometimes be discussed with certainty, is not subject to general agreement. Moore and Price (62), working on the gonad-pituitary relationship, first stated the theory that is presently most popular. This theory has been expanded so that it is now generally accepted that the secretory product of any target gland conditions the pituitary control of that target gland's activity by acting on the cells of the pituitary. Thus the level of circulating thyroxine, for example, controls the activity of the pituitary in secreting Thyrotropic hormone (TSH). This is the Moore-Price Phenomenon, or Peripheral-Humeral Effect. An opposing theory is stated by Rawson (74). He declares that TSH is inactivated by the thyroid tissue in an oxidation reaction which causes TSH to "contribute an integral part of its molecule to the metabolism of thyroid tissue." Support for this theory has been given by the work of Gallone and Galluzzi (24). They found that guinea-pigs treated with thyroid material lost all TSH activity, but that TSH injection returned them to normal. This indicates that thyroxine liberated normally leaves the thyroid in combination with the TSH which caused its release, and therefore this thyroxine has lost all antithyrotropic activity. Work with hypophysectomized rats by Cortell and Rawson (15) has shown that TSH stimulation of the thyroid was less in the presence of thyroxine than in its absence. These workers,

therefore, conclude that circulating thyroxine may diminish TSH activity before the latter reaches the thyroid, i.e., in the body fluids, not the pituitary. Barker (2), in his excellent review on thyroxine, declares that the level of this hormone controls TSH-release, but that details are lacking as to whether this is achieved indirectly through alteration of anterior pituitary metabolism along with that of all other tissues, or by some inhibition of the TSH-effect on the thyroid.

Most investigators accept the notion that greatly increased production of one pituitary hormone inhibits production of the others. Thus Selye (81) speaks of the "shift in anterior-lobe hormone production" which follows an increased need for one hypophyseal hormone. He cites as an example the decreased gonadotropin and somatropin secretion in the presence of increased corticotropin output during adaptation to stress. In support of this view, Harrow and Harrow (100) have shown that thiouracil administration caused involution of the rat adrenal, although these adrenals were still sensitive to exogenous ACTH. They suggest that this involution is due to decreased pituitary-ACTH output, resulting from excessive TSH output.

However, Halmi and Bogdanove (33) have shown that the adrenocorticotropic hormone content of the pituitary of thyroidectomized rats was not significantly different from that of normal controls. Hughes (39) declares that treatment with goiterogenic materials, which greatly increases TSH output, has no effect on gonad or adrenal weights. This is confirmed by the work of Leathem (46), Mayer (56), and Williams, et al (95). Perry (71) has administered ACTH to the intact rat, and found that iodine-uptake by the thyroid is depressed, while iodine-release is not affected. He concludes that the depressed thyroid activity is not due to inhibition of TSH by ACTH, but may be a direct effect on the thyroid. Verzar and

Vidovic (91) studied the effect of cortisone on hypophysectomized rats treated with anterior pituitary extract and TSH. Cortisone prevented the restoration of normal thyroid activity by pituitary extract and TSH. These workers declare that this is because cortisone inhibits the thyroid directly and does not interfere with TSH production.

B. Interaction between target glands. This phenomenon is being extensively studied at present, with little agreement on some points. The hormones of the thyroid and the adrenal are interrelated. Means (58) in his book on the thyroid, says that the adrenals (and the gonads) play a role in the control of the normal function of the thyroid. The effect of cortisone on the thyroid has been extensively studied. Berson and Yalow (3) have studied the effect of this hormone on the iodine-accumulating function of the thyroid. Cortisone given to euthyroid humans at 100 mg/day markedly inhibited this thyroidal function. Several other workers have gotten similar results. Versar and Vidovic (91) found that 2.5-5.0 mg. of cortisone/day prevented restoration of normal thyroid activity by TSH injection of hypophysectomized rats. Perry (71) declares that cortisone depresses radioactive iodine uptake by the rat thyroid. Similar results were obtained by Migeon (60) Kuhl and Riff (47), Versar, et al (90), and Boatman (5). Bondy and Hagewood (7) have studied the effect of cortisone on plasma protein-bound iodine (PBI) in rats. They declare that the hormone prevented the expected fall in PBI level in rats exposed to cold. This effect is interpreted as being due to cortisone-action in raising PBI blood level by decreasing PBI destruction-rate and reducing thyroxine synthesis.

Opposing the views of Berson and Yalow, work by Reiss, et al (75) shows that the subnormal I-131 uptake of the thyroids of eight humans

with Addison's Disease was increased as much as fourfold by 50-100 mg/day of cortisone. Frederickson, et al (21) agree with Gerson and Yalow's findings for euthyroids, but declare that high levels of cortisone failed to depress thyroid activity in hyperthyroidism. Gabrilove and Soffer (23) report similar results in the rat. They declare that epinephrine rather than cortisone is responsible for thyroid depression in that animal. The results of Botkin and Jensen (8) support this view.

A synergistic relationship between cortisone and TSH has been reported. Halmi (34) gives evidence that cortisone enhances TSH stimulation in hypophysectomized rats.

As far as measurable effects by cortisone on the thyroid tissue itself are concerned, there is little evidence of stimulation. Winter, et al (97) have injected 3 mg. of cortisone/day into rats over a 6-week period. A slight increase in thyroid weight was obtained with no histological change.

As for the reverse action--that of the thyroid secretion on the adrenal activity--it is agreed by most workers that such an effect exists. But there is disagreement as to the form that it takes. Selye (81) declares that heavy doses of thyroxine to the normal animal causes adrenal cortical hypertrophy. Feldman (19) agrees, and adds that in the absence of thyroxine, the adrenal of the rat decreased in size and weight. Haywood (52) has extensively studied this interaction at various ambient temperatures. He has found that at 24°C a significant increase in adrenal weight follows thyroprotein therapy, while a significant decrease is obtained with thiouracil. These results were confirmed by the work of Barrow and Barrow (100), and Freedman and Gordon (22). The effect of thyroprotein on the ascorbic acid requirement of the guinea pig has been studied by Pfander (72). Iodinated casein increased this requirement 45%.

In opposition to these findings, several workers have reported that feeding goiterogens to a variety of animals produced no effect on the adrenals. This is true of the work of Williams, et al (95), Mayer (56), Leathem (48), and Hughes (39). An interesting paper by D'Iorio and Plant (16) suggests that the thyroid affects the medulla of the adrenal, not the cortex. They report that addition of powdered thyroid to a casein-sucrose or soybean diet reduced by 50% the ability of the rat adrenal to secrete epinephrine. This was partially reversed by Vitamin B-12.

It is generally conceded that the thyroid exerts a stimulatory effect on the gonads, although there exist species differences. Maqsood and Reineke (54) report that mild hyperthyroidism stimulates sexual development in the male mouse, while hypothyroidism depresses it. Meites and Chandrashaker (59) concur, but point out species variations in thyroxine level, insofar as it is concerned with aiding gonadotropin. Richter and Winter (76) have found that feeding thyroid material to male rats causes a 27% increase in the weight of the testes and epididymis. Morris (64), as a result of work with thyroidectomised capons suggests that thyroxine and androgen exert a synergistic action on comb growth. Payne (69) also reports that thyroxine plus androgen to capons is more effective in reversing the capon effects than androgen alone. McCartney and Shaffner (57) have reported on the effect of thyroprotein on the hen. At a 0.02% level, it caused a highly significant increase in comb area.

Other workers report inhibition of certain gonadal activities by thyroid action. Herts, et al (37), have administered thyroxine and estrogen simultaneously to young chicks. This procedure suppressed the marked hyperlipemia obtained with estrogen alone. Johnson and Meites (43) have reported on the effect of thyroprotein and thiouracil on the ovaries of

female rodents. In mice, while thyroprotein significantly increased ovarian response to administered gonadotropins, the results of thiouracil administration were inconclusive. In female rats, thyroxine and thyroprotein drastically reduced ovarian response to pregnant Mare's serum (PMS) while thiouracil increased it. These results parallel those for the male rodents reported by Meites and Chandrashaker, just discussed.

There have been reports of complete lack of effect of thyroid activity on the gonads. Moreng and Shaffner (63), having treated 12-week-old chicks with thiouracil and thyroprotein simultaneously, report that testis size was unaffected, while comb growth was depressed by thiouracil alone. Comb size was maintained at normal levels by thiouracil plus thyroprotein. Galione and Galluzzi (27) have found that daily injections of thyroxine for ten days did not inhibit the gonadotropic activity of the pituitary of castrate male rats. Young, et al (99), have subjected the adult male guinea pig to thyroxine injection and thyroidectomy. They report that the sex-drive was not altered by these treatments.

There is some evidence that gonadal hormones effect thyroid activity. Money, et al (61) have found that thyroid activity is increased in the presence of testosterone, estrogen, progesterone, and other sex-hormones. But Galloni and Galluzzi (25), studying rats exposed to cold, declare that estrogen, testosterone, and gonadotropin almost completely inhibited the usual increase in thyroid activity. Others have studied the effect of estrogens on thyroid response to goiterogens. Chamorro (14) has reported that rats fed propylthiouracil plus hexoestrol showed none of the thyroid hypertrophy observed with the goiterogen alone. Chamorro's results are confirmed in another paper by Galione and Galluzzi (26). The latter say that estrogens decrease thyroid activity by inhibiting the TSH activity

of the pituitary. Some investigators present evidence for the theory that thyroid activity is not affected by gonad hormones. Odell (66), working with White Leghorn capons, declares that the thyroxine secretion-rate of these animals was not affected by the absence of gonads, or by androgen injections. Kopf (46) presents similar evidence for rats.

Observation of the virilizing effect of adrenal tumors in the human female has stimulated research into the relationship between adrenal activity and gonad activity. The evidence presented by Brimoleeome (12), indicating a positive relationship between ACTH and gonadotropin, should be mentioned. This worker declares that luteinization of the ovarian follicle by gonadotropin is augmented by ACTH, while the latter hormone inhibits follicular maturation. Ingle (40), in his review on cortisone, says that he has evidence that 5-10 mg. of cortisone/day caused regression in the size of the testes of rats. He points out, however, that work by others gives generally inconclusive evidence of any effect by cortisone on the gonads of either sex, in rats and humans.

Martini, et al (55), have studied the effect of estrogens on the rat adrenal. They say that estrogens caused a marked decrease in the ascorbic acid content of the adrenal gland of ovariectomized rats. Light and Tornahen (51) have studied the effect of androgen and estrogen on the adrenals of male rats. The adrenals were markedly enlarged after estrogen injections, while the testes were depressed. Androgen had no effect on the histology of the adrenal cortex, while estrogen caused atrophy of the zona glomerulosa with sinusoid dilation.

C. Effect of hormones on growth and metabolic rate. In general, the effect of hormones on metabolic rate and body growth rate is well known. Growth hormone secretion by the anterior pituitary has been demonstrated

in most higher animals. The growth and metabolic depression associated with thyroid deficiency is a familiar phenomenon. However, many aspects of the latter process are still under investigation. El-Ibiary and Shaffner (17) have investigated the effect of thiouracil feeding on the genetics of growth in the chick. Their results show that genetic variability does result, but is inconsistent. The relationship between temperature and thyroid effect on body weight has been studied by Maqsood and Reineke (53). They fed thyroid material and thiouracil to young male mice kept at various ambient temperatures, and found a relationship between temperature and growth response. They conclude that the tolerance limits for thyroid stimulation are determined mainly by the animal's temperature regulating capacity. Balogh (1) has shown that rats often fail to show the usual rise in metabolic rate when injected with thyroxine. He injected 0.1-0.5 micrograms, and found that one-third of his normal animals showed no immediate change in oxygen consumption. Singh and Shaffner (86) have shown that thyroid growth-control is dependent upon the caloric level of the diet of chickens. Libbe and Meites (50) have presented evidence that Vitamin B-12 and penicillin feeding can counteract the growth-depression of young chicks which normally follows thiouracil feeding. This treatment did not affect the increase in thyroid size or the decrease in comb size.

Effect of Stress

It is not proposed to discuss in detail the present theories on the roleofstress in physiological reactions. Selye (88), who is the principle proponent of the General Adaptation Syndrome Theory of stress response, gives a very complete treatment of the subject in his book, referred to above. It will be sufficient to mention here certain evidence for the effect of stress on the physiological factors considered in the present

tests. Except where indicated, the material is from Selye (81, 82), and refers chiefly to mammals.

A. Heart. Cardiac lesions do not appear after stress, if the organism successfully adapts to it. However, prolonged exposure to certain stresses, such as cold, produces fibrous nodules in the heart, if the animal is on a special diet and is unilaterally nephrectomized.

B. Metabolic Rate. It is well known that a fall in body temperature accompanies the systemic shock of early stress. This is especially evident in the adrenalectomized or hypophysectomized animal. At this time, the basal metabolic rate is subnormal, but later rises to normal.

C. Growth. Stress inhibits body growth, particularly in the very early and very late stages of the exposure.

D. Adrenals. These glands play a key role in the response to stress. It has been reported many times that in mammals the adrenal cortex enlarges under stress, due to hypertrophy and hyperplasia. The adrenal secretions are apparently necessary for a successful defense against stress, for the adrenalectomized animal is extremely sensitive to adverse conditions. Hall (32) reports that the adrenals of rats from an emotional strain are heavier than those of phlegmatic strains. Sayers and Sayers (79) have shown that the increased adrenal activity in stressed rats is directly proportional to increased ACTH output by the pituitary.

The pituitary-adrenal cortical response to stress is thought by many workers to be the cause of the metabolic changes, such as a rise in blood glucose and chloride, which appear in a successful response. Engle (41) denies that this is so, however, stating that this response is a homeostatic mechanism and "does not represent the exciting cause for many of the metabolic responses to stress." Other workers have presented evidence for theories counter to the popular one. Bullough (13) has stressed

mice by overcrowding them, and found that the adrenal size-increase was chiefly due to medullary enlargement. Hall, et al (31), have found that treatment with desoxycorticosterone acetate does not impair the pituitary-adrenal stress response. Sayers (80), in his review of adrenal cortical function, declares that sudden, temporary stress, such as a short bout of muscular exercise, produces little or no adrenal hypertrophy. He further states that treatment with the hormones of the adrenal cortex does not increase resistance to stress.

E. Gonads. Both the testes and the ovaries atrophy under stress. Sterility and estrous or menstrual irregularities have been observed.

F. Thyroid. The thyroid is said to atrophy and involute in the early stages of stress. This may be followed by hyperplasia. Bogoroch and Timiras (6) subjected male rats to forced muscular exercise for 24 hours and then measured the iodine-uptake of the thyroid. In one test, it was significantly decreased after stress. These workers point out that exercise may be like cold exposure in that it may tend to increase thyroid activity because it, like cold, influences the basal metabolic rate. In the one test in which thyroid activity receded, it is possible that the stressful effect of forced exercise predominated, and prevented thyroid stimulation by thyrotropic hormone. But Smith and Smith (88) have found that feeding mice desiccated thyroid produced a decreased exercise-tolerance. This was believed, however, to be due to a defective functional capacity of the heart, rather than to interglandular reactions.

G. Effect of Stress on the Chick. The chick has been little used as a subject for stress experiments. Its physiological response to stress is largely unknown. So far as can be determined, the first

work employing the chick as a subject for stress tests, is that of Carron (29) in this laboratory. He used New Hampshire chicks which he exposed to forced muscular exercise. Many of his tests were exploratory in nature, but they did indicate certain trends. Untreated birds exercised to exhaustion had enlarged adrenals, and slightly enlarged hearts. Thyroid, gonad, and male comb sizes were reduced, but there were large individual variations in these responses. Males were more resistant than females in a single-replicate test on sex differences. These resistant males had the largest adrenals. Other tests indicated a possible positive correlation between the ability of the thyroid to respond to thiouracil and resistance to exhaustion. Birds treated with cortisone showed a decreased resistance to fatigue, while a group treated with thyroprotein had increased resistance. Testosterone also caused increased resistance.

Histology of the Adrenal Gland of the Chick

The microscopic structure of the thyroid, gonads, and pituitary of the chick is much the same as that of mammals. The adrenal structure is like that of the lower animals (amphibia and reptiles), however. Cortical and medullary tissue are intermingled. According to Bradley (9), cortical cells "occasionally" surround the medullary cells, causing them to form independent units. Grollman (30) indicates that the chromaphil (medullary) cells always occur in groups. He says that two different kinds of cortical cells can be distinguished, on the basis of their different staining reactions. Neither of these two authors discuss the possible effect of age on adrenal histology.

Bauer and Latimer (78) have studied the adrenal of adult chickens of both sexes. They find that the cortical cells are clumped, in the center

of the gland. Kar (44) has studied the adrenals of 22-month-old Brown Leghorns. He found uniform cortical masses throughout the gland, with vacuolated cells of several different forms. The medulla was irregularly arranged in masses of 2-3 to 30-40 cells.

No information is available on the histological response of the chick adrenal to stress.

General Discussion of Methods

Purebred New Hampshire chicks were used in all but one of the tests herein reported. In one replication of one test, the chicks used had a single White Leghorn male in their ancestry. The chicks were of both sexes, and were taken at random from the University of Maryland farm flock. At hatching, they were divided into groups of 8-10 birds each and placed in electrically heated batteries having screen-wire floors. These batteries were housed in a concrete building under controlled conditions of heating and lighting. The birds were thus maintained for the duration of the tests, which extended from hatching time until four weeks of age. Food and water were available in adequate amounts at all times, except as hereinafter noted. Although different batteries in different rooms were used for each replication, the experimental groups were always arranged in the same way within the battery. The control group, receiving an unsupplemented ration, was placed at the top, and the experimental groups, receiving a ration supplement, were placed below, and arranged so that the ration having the largest supplement was at the bottom. Each group had a separate water trough.

The chicks were fed a standard starting mash. Supplements were added to this diet by means of electric mixers. Fresh feed was prepared for each replication, and was stored in metal cans with tightly fitting lids.

The nature and source of the dietary supplements were as follows:

(1) Thiouracil (74.6% pure). From Lederle Laboratories, Pearl River, New York.

(2) Iodinated casein (Protamone). Contains 0.3% chick-available L-thyroxine. From Geroghyl Laboratories, Kansas City, Missouri.

In those tests involving injection of hormone solutions, a one cc. tuberculin syringe, with a #20 needle, was used to place the hormone solution in the pectoral muscle of the chick. The nature and source of the injected hormones were as follows:

(1) Androgen (Perandren). Testosterone Proprionate in sesame oil. From Ciba Pharmaceutical Products, Inc., Summitt, New York.

(2) Estrogen. Diethyl Stilbestrol in sesame oil. From Merck and Company, Rahway, New Jersey.

(3) Gonadotropin (Conadin Serum). Extract of pregnant mare's serum, in distilled water. From Cutter Laboratories, Berkeley, California.

Just prior to sacrifice (and after exercise in the case of the stressed groups) the birds were weighed to the nearest gram on a Toledo balance. Those birds measured for metabolic rate were weighed just before this determination was made. All chicks were sacrificed at 4 weeks of age by bleeding at the neck. The carcasses were stored at -14°F for a period ranging from 24 hours to 7 days. Fifteen hours prior to autopsy, they were transferred to an environment at 55°F for thawing.

At autopsy, the appropriate organs were removed, carefully trimmed, and rapidly weighed. Small organs, such as adrenal and thyroid, were weighed to the nearest 0.2 mg. on a Roller-Smith balance. Larger organs, such as heart, were weighed to the nearest 0.01 gm. on a standard triple-beam balance.

Immediately after weighing, those tissues which were to be studied histologically were placed in Tellyesznisky's Fixative (Formol, 8.7%; 70% Ethanol, 87%; Glacial Acetic Acid, 4.3%) for preservation. For making prepared slides these tissues were imbedded in paraffin, sectioned at 10 microns with a rotary microtome, and stained with Masson's Trichrome.

Metabolic rates were measured at 4 weeks of age with the closed system illustrated in Plate 1. The birds were run in groups of four to six. Length of run was 20 minutes. The birds were taken off feed 12 hours prior to testing. Metabolic rates were calculated on the basis of the amount of oxygen removed from the system during the run, and were expressed as milliliters of oxygen removed per kilogram of body weight per hour. The chicks were sacrificed immediately after the run was made.

Stress was induced by running the birds to exhaustion in the revolving cages shown in Plate 2. The first run was made when the birds were 17-20 days of age, and the speed of revolution was 10 revolutions per minute. The experiment then proceeded as follows: Second run at 21-22 days of age; speed, 15 rpm. Third run at 24-26 days of age; speed 15 rpm. Fourth (final) run at 27-29 days of age; speed, 15 rpm. An exception to this scheme occurred in the tests involving the sex glands; this will be brought out later.

It had been noted in preliminary trials that if the birds were revolved so that they had the entire cage in which to maneuver, there was a high degree of individuality in the postural response, and consequently much individual variation in resistance to exhaustion. To eliminate this "intelligence" factor, the birds were all placed between two metal plates so arranged that the subject was forced to run straight ahead into the rotational movement of the cage. The birds were unable to turn around or to assume a sidewise stance. They were able to balance themselves somewhat by resting their wings against the plates.

These lateral panels were moved outward as necessary to allow for the increasing size of the birds as the tests progressed. They were always placed in such a way as to induce the birds to run straight ahead at

all times, but not so as to interfere with their balance. The "end-point" of complete exhaustion was taken as that time when the bird fell to the bottom of the cage and tumbled repeatedly, being completely unable to rise. Length of run was measured in minutes, and, since speed of revolution was kept constant for each of the four runs, was expressed as number of revolutions to exhaust. The initial run, at 10 rpm, was regarded as a "conditioning" run, enabling the birds to become accustomed to the cages, and its results were not used in calculating resistance to fatigue.

Investigations into the Effect of Altered Thyroid Activity on the Physiology of the Chick

A total of 275 birds (130 males; 145 females) were used in these tests. Five replications were made, over a period of three months, from April to July. The chicks were divided into six groups, on the basis of the type of diet fed, as follows:

Group 1. Negative control. Basal ration.

Group 2. Positive control. Ration contained 0.2% thiouracil.

Group 3. Ration contained 0.2% thiouracil plus 0.5 g. of Protamone per 100 lbs. of feed (cwt).

Group 4. Ration contained 0.2% thiouracil plus 1.0 g. Protamone/cwt.

Group 5. Ration contained 0.2% thiouracil plus 2.0 g. Protamone/cwt.

Group 6. Ration contained 0.2% thiouracil plus 3.0 g. Protamone/cwt.

The birds were placed on these diets at hatching. Replicates 1, 2, 4, and 5 were measured for metabolic rate. All birds were sacrificed at 4 weeks and autopsied as previously described. In addition to body weights, the weights of thyroid, adrenal, gonads, and comb were recorded.

The results of these tests are summarized in Tables I, III, and IV, and Charts 1-10, inclusive. Body weight at four weeks was greatly reduced by feeding 0.2% thiouracil. Adding Protamone to this diet increased body

weight at all levels, but body weight was always below that of the basal group under this treatment. Little difference existed between body weights at the various Protamone levels used.

Thyroid weight was greatly increased by thiouracil. There was a still greater increase in thyroid size in the group which got 0.5 g. of Protamone and thiouracil. Thyroid weight fell off in the groups which got higher Protamone levels, with the gland returning to normal size between the 2.0 and 3.0 g. levels. Considerable variation was noted in the response of the thyroid to Protamone, especially at the 2.0 g. level.

Adrenal weight was not greatly affected by the altered thyroid activity. Some size-depression was noted in the presence of thiouracil alone, and also when 0.5 g. of Protamone was fed. However, at the 1.0, 2.0, and 3.0 g. levels, adrenal size was close to that of the basal group.

Male gonad weight was not greatly affected by thiouracil treatment. However, in the presence of Protamone, these glands were considerably larger than those of the basal group. This effect was noted at all levels, but was greatest at 1.0 g.

Female gonad weight was considerably reduced by thiouracil ingestion. Addition of Protamone gradually reversed this condition, with the ovarian weight being normal at the 2.0 g. level.

In contrast to its effect on the testes, thiouracil feeding was accompanied by a great reduction in male comb size. Protamone feeding tended to increase comb size, although it was not of normal size even in the presence of 3.0 g. of Protamone.

Thiouracil treatment was also accompanied by a great reduction in the size of the female comb. The results of feeding Protamone were much the same as in the male; a tendency to increase in size without actually attaining normal size.

Metabolic rate was decreased by thiouracil. Protamone increased metabolic rate, although metabolic rate was not restored to normal by Protamone. Considerable variation was noted between replicate values in some cases.

Data on body weight, and weight of thyroid and adrenal have been calculated for the two sexes separately. These figures are presented in Table IV. Body weight was reduced by thiouracil in both sexes, with the males showing the greater proportional reduction. The females were always the smaller, but the two sexes showed proportionally equal gains in the presence of Protamone.

Except in the groups fed thiouracil alone, the females had the larger thyroids; the two sexes responded to the goiterogen with almost identical amounts of thyroid enlargement. Both sexes showed further enlargement at the 0.5 g. Protamone level. A proportional size-decrease occurred above this level.

The adrenals of the females were always smaller than those of the males. The two sexes tended to follow parallel courses with respect to these glands; a size depression at low levels of thyroid activity, with an increase in size at the higher Protamone levels. The size depression was somewhat greater in the males, however.

Investigations into the Relationships between Stress, Thyroid Activity, and the Physiology of the Chick

A total of 240 birds (120 males; 120 females) were used in these tests. Three replications were made in a period of two months, extending from the last week in August to the first week in November. The chicks were divided into nine groups, on the basis of the dietary supplementation, as follows:

Group 1. Negative Control. Basal ration.

Group 2. Positive Control. 0.2% Thiouracil added.

Group 3. 0.2% thiouracil + 1.0 g. Protamone/cwt.

Group 4. 0.2% thiouracil + 1.5 g. Protamone/cwt.

Group 5. 0.2% thiouracil + 2.0 g. Protamone/cwt.

Group 6. 0.2% thiouracil + 2.5 g. Protamone/cwt.

Group 7. 0.2% thiouracil + 3.0 g. Protamone/cwt.

Group 8. 0.2% thiouracil + 3.5 g. Protamone/cwt.

Group 9. 0.2% thiouracil + 4.0 g. Protamone/cwt.

The birds were placed on these diets at hatch. At 17 days of age, all of the birds in the nine groups were run to exhaustion in the exercise cages. This was repeated three times, as previously described, and the birds were then weighed and sacrificed at 28 days of age. During all of the exercise runs, all of the birds in the test (i.e., those remaining in the batteries as well as those actually being exercised) were taken off feed. Storage, thawing, and autopsy were as previously outlined. Observations were recorded on exhaustion time, body weight, and weight of thyroid, adrenal, gonads, comb, and heart.

The results of these tests are listed in Tables II, III, and V. In Charts 1, 2, 3, 5, 7, 8, 9, and 10, they are compared to the results obtained without stress, just discussed. Chart 6 presents the relative resistance of the nine groups to exhaustion.

Body weight was depressed in the presence of thiouracil and stress, and approached but did not attain normalcy when Protamone was fed. Chart 1 shows that these results take much the same form as did those without stress. Body weight after stress did not fall below the unstressed level until higher levels (2.0-4.0g.) of Protamone were fed.

Thyroid weight again showed a marked increase with thiouracil which was exceeded by feeding thiouracil plus the lowest level of Protamone. Additional Protamone caused the expected thyroid regression. Stress apparently had little effect on the ability of the thyroid to respond to varying thyroxine levels; Chart 5 shows that the stress curve parallels the non-stress one, and does not lie far from it at most points.

Considering the effect of the treatment on the adrenals, Chart 5 reveals that they were depressed in size below that of the controls in the presence of stress and thiouracil, were almost of normal size with 1.5 g. of Protamone, but were smaller with 2.0 and 2.5 g. Greater amounts of Protamone are concurrent with a nearly-normal adrenal size.

Chart 5 brings out strikingly the similarity in form and the dissimilarity in position of the two curves with stress the only variable. The adrenals were greatly enlarged after stress at all levels of thyroid activity, but they responded in a similar manner at the various thyroxine levels whether stress was present or not.

Male gonads were depressed in size by thiouracil, and obtained greater-than-normal size after Protamone and stress, at all Protamone levels. Chart 8 shows that the greatest divergence between the stressed birds and the non-stressed birds occurred at the 1.5 g. Protamone level, although divergence existed at 2.0, 2.5, and 3.0 g. levels. At 3.5 and 4.0 g. of Protamone and stress, the male gonads were larger than under any other treatment.

Ovarian weights also were reduced by thiouracil in the stressed birds, but Protamone treatment was accompanied by an increase to sizes above that of the control group. The greatest gain in ovarian weight was scored in the presence of 1.0 g. of Protamone. Chart 10 compares

those results with those in the absence of stress. At the 2.0 g. level the ovarian weights of the two groups are similar, but at 1.0, 1.5, 2.5, and 3.0 g., the stressed birds had larger ovaries than the unstressed birds. Those birds on the basal diet and those on thiouracil only had somewhat larger female gonads with stress than without.

Male comb weights (Chart 7) after stress showed the familiar reduction with thiouracil treatment, but increased in size in the presence of Protamone, being larger than the basal group at 1.5 g. of Protamone, and increasing sharply with additional Protamone plus stress. Little difference in average weight existed between the stressed basal group and its unstressed counterpart; the same is true in the presence of thiouracil alone. At 1.5, 2.5, and 3.0 g. of Protamone, the difference in male comb size between the stressed and the unstressed groups is marked, and the stressed birds show a continued increase above the 3.0 g. level.

Female comb weight in the stressed groups was depressed by thiouracil, but rose to supra-normal levels at 1.5 g. of Protamone (Chart 9). At higher Protamone levels, the female comb weight dropped below that of the basal group, with little variation between the various treatments. There was little difference in this determination in the basal group and in the thiouracil-treated group after stress. However, the stressed birds always had the greater average female comb weights, with this superiority being most marked with 1.0 and 1.5 g. of Protamone. No tendency was apparent for this rise to continue with higher levels of Protamone. The ovarian curves show (Chart 10) a similarity in form to those for the female combs, both with and without stress. This is not true in the case of the male reproductive factors measured.

Heart weight was below normal on feeding thiouracil to stressed birds, and remained so even in the presence of 4.0 g. of Protamone. Chart 2 shows that the hearts of the stressed birds were somewhat larger than those of the unstressed ones in the basal group, the thiouracil-fed groups and the group getting 1.0 g. of Protamone. Above this Protamone level, however, the hearts of the stressed birds were below those of the unstressed birds in size.

The average number of cage-revolutions necessary to exhaust the chicks in each group is presented in Tables IV and V, and Chart 6. The ability to resist muscular fatigue was inhibited by thiouracil, but was considerably above the normal level at 2.5 g. of Protamone. Resistance to fatigue was also high with 1.5, 2.5, and 4.0 g. of Protamone, but was low with 1.0 and 3.0 g.

The data on body-weight, weight of thyroid, adrenal, and heart, and exhaustion time were analyzed for the two sexes separately. This material is presented in Table V.

The females of each of the two experimental groups (stress and non-stress) were smaller than the comparable males at most levels of thyroxine activity. The difference is greatest however in the stressed group, and is more apparent in both groups at the higher Protamone levels. On thiouracil alone, the stressed males were smaller than the females. On the basal diet, the size of the males was apparently little affected by stress. Often chicks of one sex were larger in the presence of stress than without it. This occurs at several different thyroxine levels.

Though the female thyroid was generally somewhat larger than that of the male, especially in the presence of Protamone, the male sometimes had the greater thyroid weight in the presence of stress and Protamone.

Differences in adrenal size between the two sexes is marked at most Protamone levels in the stressed birds. The females always had the smaller adrenals. Each sex showed the same variations in adrenal size at varying Protamone levels as did the opposite sex undergoing the same treatment.

The males were always able to resist exhaustion better than the females. As for the effect of Protamone and thiouracil, it can be seen that the two sexes were roughly parallel in response, and that both resisted stress best at the 2.0 g. Protamone level. The untreated males were greatly superior to the untreated females in resisting stress. The same is true at the higher Protamone levels, especially at 4.0 g.

In the stressed groups, the males always had the larger hearts. This difference was most pronounced in the untreated birds and at the higher levels of Protamone (1.0-4.0 g.).

Studies on the Role of the Gonads in Response to Stress

A total of 174 birds (38 males and 36 females in the first test; 44 males and 56 females in the second test) were used. Two separate tests, not exact replications, were performed. In the first test, 74 birds were treated as follows:

Group 1. Positive control. 0.07 mg. of testosterone proprionate per bird injected. No exercise.

Group 2. Negative control. No injection; no exercise.

Group 3. 0.07 mg. of testosterone proprionate + exercise.

Group 4. No injection; Exercise.

All of the birds were fed the basal diet. They were deprived of feed during the exercise runs. The injections were divided into seven doses of 0.01 mg. of androgen each, every other day. These injections

commenced three days before the start of exercise. The birds were sacrificed at four weeks of age, and autopsied. The results of this test are presented in Table VI.

The body weight of the androgen-exercise group (Group 3) was not depressed as much after exercise as was that of the uninjected group (Group 4), and was close to the body weight of the control group (Group 1). Thyroid size was unaffected by androgen and exercise, but either androgen alone or exercise alone was concurrent with a reduction in size of this gland. Adrenals were enlarged to the same degree by exercise, and by exercise plus androgen. They were reduced in size with androgen alone. Although male gonads were somewhat enlarged with androgen, when exercise and androgen were given together, a weight-reduction occurred in these glands. Ovaries were somewhat reduced in size in the presence of androgen, androgen plus exercise, and exercise alone. Male combs were largest with androgen alone, and smallest with exercise alone, as were female combs. Exercise treatment saw some cardiac enlargement, both with and without androgen.

It was evident that the androgen-level used in this test was sufficient to exert only a mildly stimulatory action on the chick, as indicated by its effect on comb growth. The experimental plan was therefore altered and expanded in the second test, as follows:

Group 1. Negative control, No injection. Ten birds.

Group 2. Positive control. Exercised to exhaustion. Ten birds.

Group 3. 0.1 mg. of testosterone proprionate/bird/day injected. Twenty birds; ten exercised, ten not exercised.

Group 4. 0.2 mg. of testosterone proprionate/bird/day injected. Twenty birds; ten exercised, ten not exercised.

Group 5. 0.1 mg. of stilbestrol/bird/day injected. Twenty birds; ten exercised, ten not exercised.

Group 6. 10 units of gonadotropin/bird/day injected. Twenty birds; ten exercised, ten not exercised.

Thus there were 100 birds in this test. All were fed the basal diet. Food and water were given ad libidum, except when exercise runs were made. The injection schedule was the same as in the preceding test.

Speed of revolution of the exercise cages was increased over that previously used. The initial speed was 10 rpm., and these results not used in the calculations, as before. The second run was at 15 rpm, and the third run at 20 rpm. For the fourth run, Group 2 was exercised at 20 rpm, while groups 3, 4, 5, and 6 were revolved at 25 rpm. These changes were made necessary by the greatly increased resistance to fatigue encountered in these birds.

The results of this test may be found in Tables VII and VIII, and in Charts 11-19 inclusive. It will be seen that the birds' resistance to stress was considerably increased in the presence of androgen. However, doubling the 0.7 mg. dosage of this hormone did not significantly add to this increase. Stilbestrol administration was concurrent with a slight gain in stress-resistance but the greatest gain of all was registered by those birds which received gonadotropin.

Exercise reduced body-weight in the untreated birds. Androgen caused an increase in weight, which was eliminated by exercise. Stilbestrol had the same effect, although in this case both the exercised birds and their controls were above negative control level. It was noted that all the birds treated with this hormone acquired considerable abdominal fat. Gonadotropin also failed to protect the exercised birds from weight-loss with exercise.

Adrenals increased sharply in size on exercise, as in previous tests. This occurred in the presence of injected androgen as well as in the uninjected controls. Unexercised birds receiving androgen had adrenals which were somewhat reduced in size. In the presence of stilbestrol, the adrenals were enlarged, almost an equal amount with and without stress. Gonadotropin injection maintained the adrenals at near-normal levels in both the stressed and unstressed groups.

Testes were considerably smaller after exercise alone. Androgen caused a considerable size-reduction, which was unaffected by exercise. This size-reduction was also apparent after stilbestrol, and was here most marked with exercise. Gonadotropin stimulated male gonad growth, in both test groups.

The ovaries were unaffected by exercise alone. Androgen plus exercise caused a considerable ovarian atrophy at the 0.7 mg. level. In the presence of stilbestrol, ovarian size was reduced, and to the same degree in both test groups. Ovarian weight was lower than normal in the birds treated with gonadotropin, and a further decrease followed after stress.

Male comb weight was much less in the stressed group than in the untreated controls. Androgen always caused a marked increase in comb weights of male birds, though this was somewhat greater without added stress. The higher androgen level had a superior ability to increase comb size only in the stressed birds. Stilbestrol treatment caused a marked decrease in male comb size which was most marked after stress. Gonadotropin caused no size increase in male combs; in fact, the unexercised average was considerably below that of the negative control group. This was partly overcome after stress.

It was not possible to weigh the combs of the uninjected group of exercised females, tumbling in the exercise cages had damaged these organs too severely. It can however be seen that female comb weight was greatly increased after androgen treatment. At the lower level of androgen dosage, this effect was much less after exercise, but not at the higher level. Stilbestrol treatment altered female comb size slightly, and the exercised birds had the smaller combs. The results with gonadotropin closely resemble those with stilbestrol.

Androgen-treated birds had somewhat larger hearts than did untreated birds. It is noted, however, that this is not the case at the 0.7 mg. androgen level except in the presence of stress. The hearts of stilbestrol-treated birds were also larger than normal, both with and without stress, with the stressed birds having the smaller hearts. Gonadin-treated birds had small hearts, and this was especially true in the stressed group. It was noted at autopsy that the androgen-treated birds had hearts which were surrounded with a heavy corona of fat, and that this fat had invaded the myocardium at several points. This was also true of the stilbestrol-treated birds, but to a lesser extent.

In Table VIII, the data of this second test on the role of the sex-hormones in stress is further analyzed. Body weight, weight of adrenal, thyroid, and heart, and exhaustion time are averaged by sexes. Except in the case of the unexercised birds injected with stilbestrol, the males were larger than the females. Exercise reduced the body weight of both sexes, regardless of hormonal injection, except in the males receiving gonadotropin. As in the other tests, the female thyroid was usually the larger. Significant exceptions to this occurred with 0.7 mg. of androgen and exercise, and in both of the gonadotropin-injected

groups. Male thyroids were larger than normal in most of the treated groups, and this tended to be emphasized with stress. Female thyroids were below normal in size in most of the groups, and were smaller in the exercised groups than in their controls. Females generally had the smaller adrenals regardless of hormonal treatment, although in the presence of 1.4 mg. of androgen and exercise, adrenal enlargement was greatest in the females. Exercise caused adrenal enlargement in both sexes, with the males generally showing a greater response. In one instance (with stilbestrol) female adrenals were smaller with exercise than without. The failure of the adrenals to enlarge significantly in the presence of gonadotropin occurred in both sexes equally.

The male birds had the larger hearts. Male heart size was unchanged by exercise alone, while the hearts of the females were somewhat enlarged. In the presence of androgen, the male hearts were considerably larger after exercise than those of the unexercised males. Female heart size was larger after exercise only at the lower androgen levels. Stilbestrol treated males showed no change in heart size after exercise, while similarly treated females had smaller hearts than their controls. Gonadotropin failed to prevent some cardiac enlargement in the males after exercise, while it was accompanied by a reduction in heart size in females. Injection of 0.7 mg. of androgen was followed by a greater resistance to fatigue in the females than in the males. In all other treatments, the males were more successful than the females in resisting the stress. It should be emphasized that androgen treatment was followed by a considerably increased resistance to stress in the females, while the similarly treated males showed a comparable increase only at the higher (1.4 mg.) level of androgen administration. Stilbestrol treatment was followed by

somewhat increased resistance to exhaustion in both sexes. The gain in stress-resistance registered after gonadotropin treatment was mainly due to the males in this group, which showed the greatest increase over basal level of any group in these tests. The females of this group also showed in increased stress-resistance.

Histological Studies on the Endocrine Organs (Plate 3)

About twenty slides were prepared of thyroid and adrenal tissue, in the manner previously described. These slides contained an average of 14-16 sections, and were studied with a research-type binocular microscope at 100X, 450X, and 970X.

Thyroid tissue from normal birds was compared with that from birds on 0.2% thiouracil. It was found that thiouracil treatment was followed by a complete disruption of the typical follicular structure. The individual follicles could still be distinguished by their circular form, but were completely devoid of colloid. This material had been replaced by follicular cells, large masses of which filled the acini. These thyroids were also seen to be more vascular than normal.

The normal adrenal (Plate 3, Upper) of the 4-week-old chick was bound by a thin collagenous connective tissue sheath. Below this were numerous cell clumps of varying sizes which were scattered through a matrix composed of strands of smaller cells. These cell-clumps were sharply delimited, and appeared to be surrounded by a single layer of connective tissue. The cells were irregularly arranged within the clumps, but tended to line up at the edge. These cells had an abundant, granular cytoplasm, staining red as here treated. Their nuclei were small, vacuolated, and centrally located; they contained a nucleolus.

The matrix cells were of two types. Type one had a dense, spindle shaped nucleus and scanty cytoplasm. Type two had a round, vacuolated nucleus and a more abundant, foamy cytoplasm. In both types, the cytoplasm stained blue, with the nucleus dark, under the stain used. Occasionally, small groups of lymphocytic round-cells were seen in the matrix, especially near blood-sinuses. These latter vessels were numerous throughout the matrix.

Adrenal tissue from stressed birds was next studied (Plate 3, Lower). These slides were differentiated on the basis of the relative resistance to stress displayed by the birds from which the tissue was taken. For convenience, these two classes were designated "short-run" to indicate adrenals from birds which failed to resist stress, and "long-run" to indicate adrenals from birds which resisted stress.

In both of these classes, the normal adrenal structure just described had been completely disrupted after stress. Considerable hypertrophy and hyperplasia had occurred in both tissue elements, resulting in a dispersion of the cell-clumps. The two types of tissues were closely intermingled. Below the capsule, the matrix cells formed a rather marked band of tissue. The center of the gland was occupied by very irregular clumps of the red-staining cells, surrounded by convoluted strands of enlarged, blue-staining cells. Vascularity had increased markedly over the normal condition, and large ovoid masses of round-cells were seen at the periphery.

Microscopic differences between the "short-run" adrenal and the "long-run" adrenal was mainly one of difference in over-all size of the section. The "long-run" gland was the larger. Certain other differences were noted, however. The "long-run" gland was even more vascular than

the "short-run", with blood-sinuses and small vessels very numerous throughout. The size increase in the "long-run" gland was apparently due to hypertrophy and hyperplasia of both matrix-cells and clump-cells. The close intermingling of these two elements made evaluation difficult, but differences in staining characteristics made it appear that the size increase of the "long-run" adrenal was chiefly due to an increase in the number of blue-staining matrix cells. The clumps of red cells could be distinguished with difficulty in the "short-run" glands, while in the "long-run" glands, the matrix-tissue had completely overgrown the clumps and mingled with their cells.

DISCUSSION

Effect of Altered Thyroid Activity

Certain facts about the nature of the tests must be kept in mind while evaluating the results obtained. First, because the tests started at time of hatching, when it requires highly specialized knowledge to identify sexes in most pure breeds of chickens, both sexes were used indiscriminately in the various groups in these tests. Occasionally, a group contained a heavy preponderance of one sex, but generally they were in almost equal numbers.

Second, the time of year in which the tests were performed must be considered. This was the hot season, when thyroid activity is reported to be low. Whether this lowered activity is present in growing chicks as well as laying hens is a moot point, however. It must also be realized that thyroid activity in these tests was not physiological (except in the untreated groups) but was artificially maintained by feeding thyroprotein.

Third, the fact that thiouracil and Protamone were fed rather than injected makes their physiological levels dependent on food intake and introduces additional sources of experimental variation. However, it was desired to simulate natural conditions in these tests wherever possible. In addition, this procedure is frequently used in laboratory tests with the materials in question. Apparently, many workers feel that the variations introduced are not significant.

Fourth, it might be questioned that glandular size is necessarily a criterion of activity. There have been tests which indicate a positive correlation between thyroid weight and activity, for example (38), but others point to the nature of thyroid response to thiouracil as proof

that it is dangerous to assume such a correlation. In the present tests, since the thyroxine-secreting function of the thyroid had been superceded by exogenous thyroxine, no attempt is made to correlate size and function of this gland. Functional activity of the pituitary is the thing in question here. In the case of the gonads, an additional indication of their activity is present in the comb weights. Adrenal weights are used to evaluate the effect of thyroid hormone on them. Rather than simply assuming that there was a necessary correlation between weight and activity, the true relationship between these two factors was made one of the objectives of the tests here reported, especially in the case of the adrenal.

Fifth, although purebred birds were generally used, it cannot be denied that genetic variation influenced the results. This factor is, of course, present in any biological test, and is minimized by using inbred organisms--an unwise practice in work involving chickens due to the presence of many undesirable recessive genes in the genotype of these animals. To reduce this factor a reasonably large number of birds was used, and several replications were made to determine reproducibility. It is believed that the data here reported have a reliable degree of reproducibility.

Finally, it must be pointed out that since the present tests extended from hatching time to four weeks of age, the findings apply only to rapidly growing animals in general, and to chickens in particular. Maternal factors are important in the physiology of the young animal. It is shown in the Literature Review that species differences exist in glandular responses. These facts must be considered in the present instance.

The depression in body weight which was observed after feeding 0.2% thiouracil is a well-known reaction and is due to inhibition of the thyroid's ability to synthesize thyroxine. The depression at the higher Protamone levels is also to be expected, for hyperthyroidism interferes with growth, apparently due to systemic toxicity of large amounts of thyroxine. However, Protamone might be expected to return the body weight to normal at some level of administration. This it did not do, though the difference in body weight between the untreated group and the Protamone groups is small (Chart 1). This difference may be due to the route of administration. Some thyroprotein may become unavailable to the animal because of the action of digestive enzymes. Further, little difference existed in the effect on body weight of the various Protamone levels used. One gram of Protamone/cwt was as effective as three. This indicates that small amounts of Protamone contain sufficient thyroxine to stimulate growth to the same extent as the normal thyroid secretion does. It must be borne in mind that thiouracil was present at all times, as well as thyroprotein. The failure to attain normal growth by increasing the amount of Protamone may be due to a toxic effect by the goiterogen on all tissues. It is interesting to note in this connection that the effect on metabolic rate paralleled the growth effect (Chart 4). That is, Protamone administration increased metabolic rate but did not raise it to normal at any level. Table IV indicates that the effects of the treatment on body weight and thyroid weight are not influenced by sex.

Most of the reports on work similar to that reported here deal with the feeding of thyroprotein alone to normal chicks. Work by Wheeler, et al (94), Parker (68), and Irwin, et al (42), indicates that thyroprotein (at levels higher than those used in the present tests) increased early

growth rate. The theory that the thyroid produces more than one hormone is found in the work of Werner and Hamilton (93). They noted 15 cases of human hyperthyroidism without apparent hyper-metabolism. The work of Rivers and Lerman (77) indicates that D-thyroxine is one-eighth to one-tenth as active metabolically as is L-thyroxine. D-thyroxine may, however, be concerned with TSH-antagonism. Further work is needed to investigate this point.

In general, the thyroid gland responded to the thiouracil-thyroprotein treatment in the expected manner. It should be emphasized, however, that administration of a small amount of Protamone (0.5-1.0 g/cwt) to thiouracil-treated 4-week-old chicks caused a further increase in thyroid size over that of the chicks fed thiouracil alone. One would expect, of course, on the basis of thyroxine's known ability to oppose TSH-stimulus of thyroid enlargement, that even small amounts of Protamone would somewhat reduce the size of the goiter.

This size-increase has been noted before in this laboratory by Moreng and Shaffner (63). They used 12-week-old New Hampshire chicks. Adding 1.0 g. of Protamone and 0.2% thiouracil to the ration resulted in a median thyroid weight that was almost twice that of the group fed 0.2% thiouracil alone.

The results of the present tests as to body weight, metabolic rate, and thyroid size present the following facts which demand explanation: In normal and in thiouracil-treated animals, the TSH opposing effect and the growth-stimulating effect of thyroid hormone are apparently equal in degree. In goiterous chicks maintained on small amounts of Protamone, the growth-stimulating effect exceeds the TSH-opposing effect. In those birds on larger amounts of Protamone, the TSH- opposing effect is greater than the growth effect.

It is apparent that a different type of effect is obtained depending on whether the thyroid hormone is supplied by the thyroid gland or by exogenous thyroprotein. It is therefore suggested that Protamone supplies a growth-stimulating factor which is utilized for this purpose by the 4-week-old chick only up to a certain rather low level. The peripheral activity of this factor is further hindered by the presence of thiouracil. Also supplied is a TSH-opposing factor, which is utilized almost without limit, hence the finding in these tests that birds on the higher levels of Protamone had very small thyroids, but were slightly below normal in weight and metabolism. These two factors might be two separate functions of L-thyroxine, or one (the growth-stimulating factor), might be L-thyroxine and the other (the TSH-opposing factor), might be its optical isomer or an analogue.

An examination of the adrenal weights reveals that these glands were the smallest when TSH activity was the greatest. This indicates that the output of the adrenotropic hormones of the pituitary was inhibited by the greatly increased TSH output, thus lending weight to the theory, discussed in the Introduction, that the pituitary can secrete large amounts of only one tropic hormone at any one time, and that the Target-gland hormones act upon the cells of the pituitary. However, results involving stress, to be discussed later, indicate that this conclusion is erroneous. A more likely explanation of the adrenal weight reduction is that the metabolic activity of these glands is especially reduced in hypothyroidism. Some weight reduction at high Protamone levels, noted both with and without stress, shows that these glands are sensitive also to high thyroid-hormone titers. Thus the experimental results presented here support the contention of Selye and others, mentioned in the Literature Review,

that thyroxine has a stimulatory effect on adrenal size. They do not, however, support the view that high levels of thyroxine cause adrenal hypertrophy.

Although Protamone administration was followed by an increase in male gonad size above that of the untreated group, it is doubtful that any special significance can be given to this. Variations in the control-group replicates makes the pooled average of this group low. It is this depression, rather than any great increase after Protamone which is responsible for the amount of difference. It appears, therefore, that male gonad size was decreased by thiouracil, but reached its highest levels in the presence of reduced thyroxine activity.

Activity of the testis, as measured by male comb weight, was drastically reduced in the absence of thyroxine. Addition of Protamone caused male combs to attain near-normal size. There is, therefore, little indication of correlation between testis size and activity. Both hypo- and hyper-thyroidism depress activity, with hypothyroidism having the greatest effect. The results indicate that normal testis stimulation of secondary sex characters depends on a normal amount of circulating thyroxine. This effect might be due to either (1) dependence of the level of gonadotropin secretion on the level of TSH output, or (2) a direct effect by the thyroid hormone on the tissues of the testis and comb. The fact that male comb size fails to reach normal in the presence of thiouracil and Protamone is probably due to the toxic effect of thiouracil previously mentioned.

Ovarian and female comb weights show a much closer correlation than do their male counterparts. Hypothyroidism depresses ovarian size, which is increased by Protamone. Gonadotropic activity in the female chick,

as measured by ovarian size and activity, is therefore apparently dependent on thyroid activity. As in the case of the males, it is therefore necessary to conclude that these results are due to either (1) dependence of the gonadotropin level on TSH output, or (2) a direct effect by thyroxine on ovary and comb. As will be brought out in the discussion on stress-effects, the latter explanation is favored, for both sexes. Nalbandov (65) states that the ovary of the chick is refractory to gonadotropic stimulation until just before sexual maturity. If this is true, then gonadotropin involvement in the female chicks of the present test is ruled out.

In summary, Protamone caused more metabolic stimulation than TSH-opposition at very low levels, an effect which was reversed at higher levels. This is attributed to a dual nature of the factor or factors provided. Adrenal weight, and weight and activity of the gonads, were directly proportional to thyroid activity, indicating direct action by thyroxine on the sex glands. These effects were somewhat opposed by the toxic action of thiouracil.

Effect of Stress and Altered Thyroid Activity

The facts mentioned at the beginning of the discussion on the non-stress tests, just preceding, are equally applicable here. Sex effects, time of year, route of administration of the drugs, genetic factors, and age limitations all must be considered. It should be mentioned that these stress tests were carried out at a different time of the year from the previous series--when the average temperature is lower. In addition, although the type of stress chosen--muscular exhaustion--is generally called "non-specific", it is doubtful whether any stress could be so

designated. Exercise fatigue, for example, is more directly related to certain physiological systems than to others. Muscular development and efficiency affects resistance, as does circulatory and respiratory efficiency. It is even possible that learning ability enters into the picture, for it was necessary for the birds to learn to balance themselves in the revolving cage, and to adopt the most efficient response to the enforced exercise. The preliminary "conditioning" run was made to offset the effects of this factor. It is felt, also, that the presence of the lateral plates, which forced all of the birds to make the run in the same position, eliminated an important source of variation that may be associated with learning ability. Thenumber of "extreme" individuals--those running a very short or very long time--was reduced.

The question arises as to how the endocrine system may be involved in the response to muscular exhaustion, and how some of its products may enhance resistance. Assuming that no pathological conditions exist, it is known that in the untreated human the resistance to exercise fatigue is not dependent upon the muscles themselves, nor on metabolic fuel-supply, blood oxygen transport, or respiratory efficiency. The only body-system remaining which could possibly be involved is the circulatory system. An inspection of the literature reveals that physiologists believe that the compensatory power of the heart and circulation sets the limit to capacity for exercise.

Thus the most significant increase in exercise-tolerance would be accomplished by a beneficial effect on the heart muscle and the vessels of the circulatory system. It cannot be assumed, however, that the other factors mentioned are insensitive to stimulus, and are incapable of increasing their activity in the presence of humoral factors, to add to

the resistance obtained. The circulatory factor is the principle one, but not the only one.

Epinephrine, the hormone of the adrenal medulla, is known to affect directly the circulatory system, particularly in response to exercise. Increased pulse-rate and vasoconstriction responses are due to the action of this hormone. However, vascular responses vary. Constriction occurs in skin and viscera, while heart and skeletal muscle vessels are dilated for greater blood supply.

Thyroxine has a similar action. It has a direct cardiotropic effect, producing increased pulse-rate, blood pressure, cardiac output and heart size.

Certain hormones of the adrenal cortex, at high levels, have been shown to cause enlarged hearts and increased blood pressure.

Estrogen has a vasodilator action that is well-known, and other actions are suspected along similar lines. Androgen acts similarly.

As for the systems and factors other than the circulatory which may be involved in response to exercise, adrenaline increases rate and depth of respiration, and relaxes the muscles of the bronchioles. It is also known to exert a beneficial action on the skeletal muscles, causing a postponement of fatigue and increased work capacity. However, its role in thus increasing muscular efficiency is questionable.

Thyroxine apparently has a beneficial action on muscular strength at physiological levels. High levels of this hormone have the opposite effect.

Androgen is believed to be responsible for the superior musculature of the male of most species.

The endocrine system is known to be important to the function of the metabolic and oxygen transport systems. Any increased endocrine

activity that might tend to stimulate muscle metabolism by increasing lactate metabolism or raise the levels of glycogen, glutathione, and myoglobin, would increase resistance to fatigue. This is true for the muscles involved in respiration as well as those used in locomotion, and also for the cardiac muscle.

Anterior pituitary and adrenal cortical hormones are known to be involved in metabolic systems. Their exact roles are in dispute, however, with current theories shifting rapidly in response to new findings in this active field of research. Some workers believe that these hormones accelerate glyconeogenesis by influencing either phosphorylation reactions or deamination. A pituitary hormone controls the level of glycogen-glucose conversion in the liver. An adrenal hormone is also apparently involved, while the involvement of thyroxine in this response is also suspected.

Epinephrine accelerates production of glucose by the liver, and increases lactic acid levels in the tissues. The adrenal cortical hormones stimulate production of glucose from non-carbohydrate sources, and apparently check the combustion of this sugar. Insulin has long been known to inhibit glucose production, by blocking glycogen breakdown and production.

Exercise increases red blood cell count. Physiologists believe that this is accomplished not by increased production of circulation of the erythrocytes, but by hemoconcentration due to a shift of fluid from the blood-vascular system to the intercellular spaces. Certain adrenal cortical hormones are known to be important in water metabolism and distribution. These hormones strongly affect capillary permeability and excretion of mineral salts. Thus increased activity by these hormones would increase the total oxygen-carrying capacity of the blood.

Turning now to an appraisal of the results obtained in the present tests, an examination of Chart 1 shows that the body weights of all birds fed thiouracil and Protamone were less after this treatment than the body weight of untreated birds. This occurred both in the presence of stress and in its absence. This is believed to be due to the toxic action of thiouracil. It is evident, however, that the birds which associated growth depression in the presence of stress were either normal or hypothyroid, for exercise depressed body weight below that of the unexercised groups only at higher Protamone levels.

The hypothyroid groups in this test were on thiouracil, and their thyroids were therefore unable to synthesize thyroxine. It is thus necessary to look elsewhere for the cause of the growth response observed in these groups. Reference to Chart 5 shows that the growth response is paralleled by the increase in adrenal size in these groups, after stress. Although it is well known that adrenalectomy inhibits growth, it has never been shown that cortical hormones are concerned directly with this process (89). It is suggested instead that increased adrenal activity exerted a beneficial effect on growth in the present tests, by its general systemic effects on salt metabolism and sugar metabolism. These effects were most obvious in normal birds and in hypothyroid birds. They were counteracted by high levels of circulating thyroxine, apparently due to this hormone's toxic effect on adrenal activity. This effect was most pronounced in the females (Table 5), which may be due to the greater sensitivity to thyroxine in the female.

So far as thyroid weight is concerned, there is no indication that the thyroid gland took part in the response to stress, of the basal group (Chart 3). However, this may merely be an indication that size is

no necessary criterion of activity in this gland. In the treated groups, weight change after stress does not indicate intervention on the part of the thyroid, since the activity of this gland is nullified by thiouracil.

Stress effected a more profound change in the adrenals than in any other tissue studied (Chart 5). The same increases in size is a familiar response in mammals under stress. The present tests show that the young chick responds in a similar manner.

Since it has been reported many times that hypophysectomy inhibits the adrenal cortical response to stress (81), it is obvious that the factor responsible for adrenal enlargement is adrenocorticotrophic hormone (ACTH). In the present tests, therefore, a marked increase of ACTH secretion was effected by stress at all levels of thyroprotein treatment. In those groups which got little or no thyroprotein, the thyrotropic hormone production was necessarily also high, to maintain the enlargement of the thyroids which was noted. Thus it must be concluded that the pituitary can secrete greatly increased levels of two trophic hormones simultaneously.

The observation that the pituitary can secrete high levels of two hormones simultaneously leads to certain other conclusions. It has been mentioned in the Introduction that many investigators believe that the hormones of the target glands act on the cells of the pituitary to control its hormonal output. It is assumed that the pituitary secretes a relatively fixed amount of total hormone, and that variations in the level of any component hormone affect the levels of the other components. But since it has been shown in the present tests that two component hormones can greatly increase in output simultaneously, without noticeably disturbing the levels of the others, it is obvious that either (1) the

pituitary can greatly increase its total hormonal output, or (2) control of the level of effective anterior pituitary hormone takes place outside of the pituitary--either in the body fluids or in the target glands. This latter process would be one in which the target gland hormones deactivate the pituitary hormones, rather than influencing the activity of the cells which produce them. Disturbance of any one of these deactivation phenomena should have no necessary effect on any of the others.

Although the activity of any organ can vary considerably, there are physiological limits beyond which this activity cannot go. It is likely that this is true for the pituitary as well as for other organs. Therefore, the explanation for the control of pituitary activity offered under (2) above is favored over that given under (1).

It is interesting to note a similarity in the form of the two curves in Chart 5. This indicates that whatever effect thyroxine concentration had on adrenal activity was exerted and responded to regardless of other factors, such as stress. The failure of the adrenal glands of the stressed birds on Protamone to attain the size of the glands of the basal group (although they approached this size very closely at one level) is attributed to (1) the toxic effect of thiouracil, and (2) in the "hyperthyroid" groups (2.0-4.0 g/cwt) to added toxicity of the high thyroxine levels.

An examination of the recorded data on individual birds leads to the conclusion that, at all levels of thyroxine activity, adrenal enlargement is usually associated with an increased resistance to stress. However, it is noted that while those birds which best resisted stress were always among those having the largest adrenals, this adrenal size-increase was no guarantee of a successful resistance. Birds with large

adrenals sometimes failed to perform well in the exercise cages. But birds which showed the least adrenal enlargement were never able to withstand stress well. Therefore adrenal enlargement is associated with an enhanced resistance to stress in the present tests, but this enhancement is sometimes interfered with by unknown factors. One of these latter may be a failure to acquire the ability to maintain balance in the exercise cage, for which purpose the first run was made. Another may be that increased size of an endocrine organ is not necessarily related to increased activity. The results obtained indicate that this is true in the case of the adrenal.

A significant lack of correlation exists between adrenal enlargement and resistance to fatigue when the data are considered by groups. Comparison of Charts 5 and 6 shows that some groups, such as those on 2.0 and 2.5 g. of Protamone, which showed the least average adrenal enlargement were able to resist stress very well--better, in fact, than the untreated group. Further, several of the treated groups (1.5, 2.0, 2.5, and 4.0 g.) were able to withstand stress better than the untreated birds. This is contrary to the finding on adrenal enlargement, which in the treated groups never exceeded that of the normals.

It is postulated that these findings indicate the following facts: (1) Thyroxine level may have effected the exhaustion resistance. All of the treated groups were smaller in body weight than normal, but most resisted stress better than did the normal group. The Protamone-group which resisted stress most successfully (2.0 g.) was made up of birds which were the smallest of any group at the end of the tests. Birds fed 4.0 g. of Protamone resisted stress well. It is suggested that the amounts of thyroxine provided by the Protamone levels used were sufficient

to increase resistance to stress to above-normal levels. (2) Although a positive relationship exists between adrenal enlargement and resistance to stress, it is not a quantitative one. This illustrates the general principle, just mentioned, that gland size is not a necessary criterion (but a good indication) of activity.

The fact that cardiac enlargement did not accompany stress at any level (Chart 2) indicates (1) that the circulatory system of the chick adapts to acute, short-term stress as does that of mammals, and (2) the amount of hyperthyroidism (if it can be so designated) present was not sufficient to cause cardiac damage. In fact, it is possible to say that the heart-response indicates that the conclusions drawn from the results of thyroid weight and body weight are true, and that in these tests, the animals were all either metabolically normal or hypothyroid. Those groups on higher Protamone levels actually had reduced heart size. A close correlation between heart size and body weight is noted. Thus the toxic effects of thiouracil and thyroxine on general tissue development are reflected by heart size, rather than any specific treatment effect on the organ itself.

The most apparent effect of stress on gonad and comb weights was its production of an increase in these factors, especially at higher Protamone levels. A close correlation existed between ovarian weights and female comb weights after stress.(Charts 9 and 10), indicating that the combs accurately reflected ovarian activity changes. The shape of both curves is similar to that previously found for body weight, adrenal weight, and heart weight. This indicates that ovarian and comb size reflects the effect of the treatment on the body as a whole. However, the similarity between adrenal response to stress and response of ovaries and combs,

and the apparent increase in ovarian activity after stress, indicates that adrenal secretion has had a positive effect on the female reproductive system. This may be either a direct, androgen-like effect on the female comb, or a stimulation of the androgen-secreting activity of the ovary. The ovarian enlargement observed may indicate that it is the latter which occurs, although it is not impossible that both take place.

The male gonads and combs showed a similar response to stress, although a marked increase in the size of both organs was noted in the Protamone-treated groups (Charts 7 and 8). This cannot be accounted for on the basis of adrenal activity alone, since this latter factor showed no tendency to rise along with increased thyroxine levels. It is apparent, therefore, that thyroxine had a stimulatory effect on testis growth, and especially on male comb growth, in the presence of increased adrenal activity. This effect did not occur in any other tissue. Thus we may conclude that (1) thyroxine acts synergistically with some adrenal factor to stimulate male reproductive development, and (2) increased androgen activity may be a part of a successful response to stress.

It should be pointed out again that male chicks had greater body weights, smaller thyroids, larger adrenals, and larger hearts than their comparable females, both with and without stress (Table V). However, it is noted that these differences are sometimes increased after stress. Body weight reduction in the Protamone-treated groups was influenced chiefly by the small size of the females. Thus the adverse effects of stress on growth were most pronounced in the females.

The ability of the female thyroid to respond to TSH, which normally exceeds that of the male thyroid, is accentuated by stress in the presence of High TSH levels, but is below that of the males at low TSH levels (high

thyroxine levels). It is believed that this is an indication of stimulation of metabolism of the thyroid tissue of both sexes by cortical hormones. The size reduction at higher thyroxine levels may be related to reduced body size.

The sex differences in adrenal weights indicate that both sexes responded markedly to stress with adrenal size-increase, though the increase was somewhat more marked in the males. This greater adrenal size is undoubtedly responsible for the greater ability of the males to resist stress at all thyroxine levels, though their superior muscular development to start with must also be a factor.

Summarizing the effects of stress, a marked adrenal enlargement was produced, which was indicative of but not necessarily allied with an increased adrenal hormone secretion. These hormones, in conjunction with thyroxine, caused an increased stress resistance, growth rate, and reproductive development in both sexes. The effects varied according to the level of circulating thyroxine, and were influenced by thiouracil toxicity. Sex differences in body weight, thyroid size, adrenal size, and resistance to fatigue were due to interaction of sex differences in physiology of the thyroid and skeletal muscles with increased adrenal activity.

Effect of Sex Hormones on Resistance to Stress.

The general comments about exercise stress which were made in the previous discussion are applicable here. However, the remarks concerning administration of Protamone and thiouracil do not apply, for the hormones used in the present tests were injected. A more constant and uniform level can therefore be assumed.

It is apparent from the results of the first test (Table VI) that adding to the titer of circulating androgen increased slightly the resistance to fatigue. The increase was to the extent of about 100 revolutions, on the average, and is therefore not considered to be a marked response, but only an indication that the treatment had had a favorable effect.

The reduction in thyroid size in the presence of added androgen indicates the existence of a direct effect of androgen on thyroid tissue. A similar action of the adrenal hormones is indicated by the observation that exercise alone was followed by a reduction in thyroid weight. These results are like those obtained at higher androgen levels, to be discussed later. No explanation can be offered for the failure of stress and androgen together to cause thyroid weight reduction in the present test, although they did so at the higher androgen levels.

The androgen treatment in this first test apparently had no effect on the ability of stress to elicit adrenal enlargement.

The fact that the male gonad was not reduced in size in the presence of 0.07 mg. of androgen indicates that this level was not sufficient to cause the expected repression of gonadotropic activity. The greater testis size in the androgen-treated group over that in the control group results from the presence in the former group of one bird with very large testes.

The ovaries, however, were inhibited by androgen, indicating that this hormone opposed the gonadotropic stimulus on their growth.

The androgen was sufficient to stimulate comb growth in both sexes, which shows that this tissue is very sensitive to male hormone. The smaller size of these organs in the presence of exercise is due to damage resulting from tumbling in the exercise cages.

In beginning the discussion on the second of the two tests involving sex-hormone injections, it must be emphasized that, since the speed of revolution at which these birds were exercised was greater (in the latter runs) than that employed in any previous test, the degree of stress represented by the number of revolutions to exhaust is not exactly comparable to that in the previous tests involving Protamone and thiouracil. The test presently under discussion was therefore not initiated as a replicate of the stress applied in the Protamone-thiouracil tests, or in the preliminary sex-hormone test, but as an independent test, in this respect. It is doubtful, however, that the physiological responses involved are different at the different speeds of revolution, since the end-point was the same in all cases--complete exhaustion. A high blood lactate and high oxygen debt would be expected, therefore, to occur in all subjects.

The results obtained in the second test (Tables VII and VIII; Charts 11-19 inclusive) show that androgen, estrogen, and gonadotropin each failed to protect against weight loss after exercise-stress. This occurred in both sexes. It is evident that the sex-hormones did not act on the pituitary to increase secretion of growth hormone. But the fact that thyroid size is markedly depressed after stress and androgens, while adrenal size is increased, indicates that a hormonal interaction is involved. The following explanation for these results is offered: The injected androgens, and the adrenal hormones greatly increased levels of which are stimulated by stress, act together upon the thyroid tissue to stimulate its thyroxine output. This high thyroxine level inhibits TSH secretion, resulting in smaller thyroids. This reaction is most marked in the females, which did not show their usual marked thyroid

size superiority after stress. This is another indication of the greater sensitivity of the female thyroid to TSH.

The failure of stilbestrol and gonadotropin to incite a thyroid size-reduction is apparently related to the failure of the adrenals to enlarge after stress in the presence of these hormonal elements. However, it is possible that this apparent failure is due rather to a condition of adrenal enlargement existing in the unstressed birds of these groups (Chart 13). This is the case after stilbestrol, so that we must conclude that this synthetic female hormone constituted a systemic stress. The same thing is true of gonadotropin, though to a lesser extent.

The effect of the hormonal treatment, both with and without stress, is as would be expected in view of the Moore-Price theory. Increased androgen levels caused decreased gonad size. This is because the increased levels of the gonadal hormone decreased the gonadotropin level. It is noted that stress had no effects which altered this picture. The thyroid effects which have just been discussed are possible because of the fact that the present treatment included no alteration of the TSH-thyroxine balance, as was the case in the previous tests. No thiouracil was present to inhibit thyroid activity.

As for comb size, stress seemed unable to modify the expected response materially. The reduced size at the 0.7 mg. level of androgen is probably due to damage resulting from tumbling in the exercise cages. The depressing effect of stilbestrol on the combs of both sexes, with and without stress, and concurrent with a body weight increase, indicates that a specific action of the hormone is involved, rather than the mere reflection of body-size changes. Stilboestrol apparently reduces gonadotropin output, thereby limiting androgen production.

The failure of the combs of both sexes to respond to exogenous gonadotropin administration indicates (1) that the testis does not respond markedly to gonadotropin stimulation with greatly increased androgen output, without the presence of another factor, and (2) that the ovary is refractory to this treatment. This other factor may be an increased output of thyroxine and adrenal hormone which act together on androgen-producing cells.

The apparent cardiac enlargement after stress at the 0.7 mg. level of androgen is due to the greater response of the male hearts to exercise stress. This apparently is not a successful adaptation to stress, for very little enhancement in exhaustion time over the basal group is noted. In addition, these males were less able to withstand stress than their comparable females. It will be recalled that the androgen treated groups had fatty hearts. Thus the male hormone, as well as the female hormone, has exhibited a lipotropic action, especially at a lower level of injection. The androgen effect was localized, however, being especially pronounced in the heart, while the stilbestrol induced fat deposition was more general. The cardiac fat deposition was increased after exercise in the androgen-treated male. This suggests that adrenal hormones may have been involved in stimulating fat deposition.

In spite of the adverse effect of androgen on the male heart, its overall effect was to enhance markedly the resistance to stress of all the exercised birds (Chart 14). However, reference to Table VIII shows that the major reason for this overall effect was not a great increase in male resistance at all levels, but rather was due to such an increase on the part of the females. We may postulate therefore, that the higher androgen titer in the males caused more serious fat damage to their hearts

than that occurring in the females. This effect is apparently overcome by greatly increasing the androgen level; the stimulatory effect of the hormone on muscular efficiency more than offsets any possible adverse effect on the heart at 1.4 mg. of androgen. Also, it is evident that since the females lack great amounts of androgen-producing tissue, they might be expected to show a sharper response to exogenous male sex-hormone. Their androgen titer is normally much farther from the hypothetical upper limit than is the male titer.

It is worthy of note in this connection that doubling the amount of androgen injected (from 0.7 mg. to 1.4 mg.) did not greatly increase the resistance to stress. It is apparent, therefore, that physiological limits do exist as to the response which the organism can make to any hormone. For the four-week-old chick, this limit exists at that concentration produced by 0.7 mg. of androgen. This is especially true of the female.

Such physiological "ceilings" are well-known to the endocrinologist. It is worthy of note, however, that they play a part in limiting response to stress, and also that they are not appreciably altered by stress.

The great increase in resistance to fatigue after gonadotropin is especially marked in the males, but not insignificant in the females. Gonad and comb size in the gonadotropin-treated groups do not indicate any increased androgenic activity as a result of this treatment. There is very little adrenal enlargement. Hearts are smaller than in any other group, showing that this organ had not adapted to the stress by enlargement. Thyroid size is like that of the other groups in the test. It must therefore be concluded that the increased resistance to stress exhibited by this group of chicks is due to some factor not measured in the

present observations. The presence of contaminants in the injected preparation cannot be ruled out.

Summarizing the effect of sex-hormones on stressed birds, androgen and adrenal hormones caused increased thyroxine production in stressed birds, while stilbestrol acted as an added stress. Gonadotropin caused increased stress-resistance, but the mechanism by which this was produced is not known. High androgen levels caused fatty infiltration of the heart, which was not sufficiently damaging to offset the marked stress-resistance induced.

Histology of the Adrenal

The observations on the normal adrenal show that the microscopic structure of this gland in the young chick closely resembles that reported for more primitive forms, such as the lizard (89). The "matrix" cells described in the present paper are cortical, and they surround many sharply discrete units of medullary cells, which are more regularly arranged than has been reported for adult chickens.

The observations on the stressed adrenal show that both medulla and cortex respond to stress with hypertrophy and hyperplasia, increased vascularisation, and lymphocytic invasion. Although the nature of the tissue relationships in the chick adrenal make definite conclusions difficult to arrive at, it appears that the young chick is chiefly dependent on the cortex for stress-resistance, but to a lesser degree than are mammalian forms. Intensive histological and cytological studies are needed to clarify this point.

CONCLUSIONS

Thyroprotein at very low levels has little power to affect the activity of thyrotropic hormone in goiterous chicks, but does possess growth-stimulating properties. At high levels, thyroprotein is more active in opposing thyrotropic hormone than in stimulating growth in the presence of thiouracil. This may be due to toxic action of thiouracil, however. Thyroprotein provides two unequal effects, one of which is the opposition of the thyrotropic hormone, and the other of which is the stimulation of metabolism.

The adrenal glands of the chick enlarge in response to stress, and this enlargement is indicative of, but not always allied with, a successful response. Thyroxine aids in the resistance to stress.

Thyroxine stimulates gonadal growth, while androgen and the adrenal hormones stimulate thyroid activity.

Androgen increases the ability of the chick to resist stress. Gonadotropin also is active in this respect, but the mechanism of action is not apparent.

The size of endocrine organs is not necessarily a measure of their activity. However, increased activity is usually associated with increased size of the adrenals, thyroid, and gonads.

The adrenals of the chick respond to stress with hypertrophy and hyperplasia of both cortical and medullary elements, with overall size-increase being somewhat greater in the cortex.

The pituitary of the chick is capable of secreting high levels of thyrotropic hormone and adrenocorticotropic hormone simultaneously. Therefore, the output of any pituitary hormone is not necessarily conditioned

by the output of any other, and it is likely that control of the level of pituitary hormones by target-gland hormones occurs apart from the pituitary itself.

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TABLE I

Replicate Mean Values of Body Weight, Weight of Thyroid, Adrenal, Gonads, and Comb, and Metabolic Rate of New Hampshire Chicks on Normal Diet and on Diets Containing Thiouracil Plus Graded Levels of Protamone

	% Thiouracil					
	0.0	0.2	0.2	0.2	0.2	0.2
	Gms. Protamone/cwt					
	0.0	0.0	0.5	1.0	2.0	3.0
Replicate	Body Weight, Gms.					
1	263 ± 11.4	153 ± 5.6	250 ± 12.4	260 ± 14.4	249 ±	2 ± 8.1
2	350 ± 8.2	202 ± 12.2	275 ± 15.4	299 ± 18.8	324 ±	0 ± 10.8
3	349 ± 11.1	216 ± 9.7	321 ± 9.1	342 ± 9.8	322 ±	5 ± 13.7
4	352 ± 12.0	227 ± 7.3	298 ± 13.1	314 ± 11.3	307 ±	2 ± 9.3
5	307 ± 15.8	241 ± 21.1	286 ± 14.9	290 ± 6.3	308 ±	5 ± 9.0
Replicate	Thyroid Weight, Mg.					
1	18.6 ± 1.0	79.7 ± 3.6	128.0 ± 30.3	62.8 ± 16.9	10.5 ±	2 ± 0.7
2	20.7 ± 2.3	242.2 ± 53.5	285.7 ± 49.8	259.6 ± 31.8	67.6 ± 2	6 ± 2.2
3	22.6 ± 1.9	228.5 ± 63.1	212.8 ± 54.7	134.1 ± 13.4	11.2 ±	8 ± 7.1
4	19.3 ± 1.8	172.7 ± 32.0	208.6 ± 30.6	166.5 ± 27.2	20.6 ±	2 ± 3.1
5	21.3 ± 4.1	185.6 ± 28.2	215.9 ± 36.2	162.6 ± 21.9	63.9 ±	6 ± 1.7
Replicate	Adrenal Weight, Mg.					
1	26.4 ± 3.0	22.5 ± 1.7	19.9 ± 2.6	26.9 ± 1.8	24.0 ±	1 ± 5.3
2	28.6 ± 2.4	23.0 ± 1.8	23.8 ± 7.2	27.3 ± 1.8	33.9 ±	2 ± 4.6
3	29.8 ± 1.7	28.4 ± 6.8	30.3 ± 2.0	32.5 ± 3.2	23.0 ±	3 ± 2.3
4	33.5 ± 2.4	28.4 ± 2.0	29.2 ± 2.6	34.5 ± 3.4	29.8 ±	8 ± 4.7
5	26.7 ± 1.6	25.3 ± 3.0	27.0 ± 2.1	30.0 ± 1.1	27.0 ±	7 ± 2.2
Replicate	Male Gonad Weight, Mg.					
1	48.9 ± 8.0	55.6 ± 8.9	56.5 ± 11.4	63.3 ± 9.5	61.6 ±	3 ± 21.6
2	70.9 ± 7.8	52.3 ± 6.7	68.9 ± 23.7	77.9 ± 20.4	68.7 ± 1	9 ± 8.1
3	96.5 ± 8.8	63.4 ± 10.2	94.6 ± 4.8	88.2 ± 10.6	85.1 ±	7 ± 2.9
4	78.9 ± 5.3	104.1 ± 31.1	74.2 ± 7.7	89.6 ± 7.2	74.8 ±	0 ± 4.9
5	54.0 ± 8.0	64.0 ± 4.2	80.9 ± 10.3	84.8 ± 14.4	69.1 ±	5 ± 6.3
Replicate	Female Gonad Weight, Mg.					
1	46.3 ± 3.1	36.2 ± 3.4	47.8 ± 7.3	52.1 ± 4.2	59.2 ±	4 ± 9.5
2	63.1 ± 6.3	23.5 ± 5.3	46.7 ± 6.5	46.8 ± 2.3	59.9 ±	3 ± 6.4
3	70.2 ± 7.8	37.2 ± 3.4	55.0 ± 6.0	60.8 ± 3.8	79.0 ± 1	2 ± 3.8
4	69.1 ± 4.0	40.7 ± 2.3	55.6 ± 3.4	42.9 ± 4.7	58.8 ±	8 ± 2.0
5	60.3 ± 3.4	40.0 ± 3.7	56.7 ± 9.1	56.1 ± 1.4	60.7 ±	9 ± 5.8

Table I (Cont'd)

Replicate	Male Comb Weight, Mg.									
1	170.2 ± 25.1	24.4 ± 4.5	154.1 ± 44.0	180.2 ± 54.5	152.5 ± [illegible]	[illegible] ± 35.7
2	220.7 ± 19.7	21.1 ± 2.3	108.6 ± 74.8	112.5 ± 37.5	145.1 ± [illegible]	[illegible] ± 127.9
3	359.3 ± 56.6	28.2 ± 4.2	190.5 ± 25.8	230.9 ± 51.7	299.0 ± [illegible]	[illegible] ± 28.2
4	257.2 ± 42.0	36.0 ± 4.4	122.4 ± 15.8	159.6 ± 25.5	218.8 ± [illegible]	[illegible] ± 29.5
5	253.6 ± 44.2	31.5 ± 10.9	125.7 ± 19.9	179.1 ± 26.6	100.8 ± [illegible]	[illegible] ± 60.2

Replicate	Female Comb Weight, Mg.					
1	52.3 ± 9.8	10.9 ± 1.4	35.6 ± 4.3	43.6 ± 1.5	49.6 ± [illegible]	[illegible] ± 0.9
2	70.3 ± 7.3	20.4 ± 3.1	39.6 ± 6.1	57.3 ± 5.9	62.7 ± [illegible]	[illegible] ± 7.8
3	70.0 ± 5.0	24.4 ± 3.0	41.2 ± [illegible]	57.1 ± 7.2	[illegible] ± [illegible]	[illegible] ± 5.3
4	80.3 ± 10.8	25.4 ± 2.1	40.7 ± 3.3	51.6 ± 5.1	47.8 ± [illegible]	[illegible] ± 9.7
5	65.5 ± 4.1	23.7 ± 4.0	34.4 ± 8.2	53.4 ± 1.7	65.8 ± [illegible]	[illegible] ± 6.0

Replicate	Metabolic Rate, Ml./Kg./Hr.					
1	3199	2358	2867	2456	2731	[illegible]
2	1642	1316	1484	1768	1952	[illegible]
4	1671	537	899	1059	960	[illegible]
5	860	922	1195	1011	1256	[illegible]
Pooled Mean	1843	1283	1611	1573	1274	[illegible]

TABLE II

Replicate Mean Values of Body Weight, Weight of Thyroid, Adrenal, Gonads, Comb, and Heart, and Resistance to Exhaustion of New Hampshire Chicks Exposed to Stress While on Normal Diet and on Diets Containing Thiouracil and Graded Levels of Protamone

	% Thiouracil								
	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Gms. Protamone/cwt								
	0.0	0.0	1.0	1.5	2.0	2.5	3.0	3.5	4.0
Replicate	Body Weight, Gms.								
1	353 ± 13.9	214 ± 4.2	319 ± 10.9	340 ± 11.4	334 ± 17.1	285 ± 15.3	281 ± 10.6	286 ± 12.0	316 ± 14.8
2	328 ± 18.5	240 ± 10.2	304 ± 11.9	301 ± 12.6	275 ± 9.8	281 ± 14.4	305 ± 10.7	294 ± 7.1	299 ± 11.5
3	305 ± 24.3	256 ± 8.3	318 ± 10.1	296 ± 15.6	273 ± 13.0	290 ± 11.7	305 ± 12.3	271 ± 10.5	299 ± 7.5
Replicate	Thyroid Weight, Mg.								
1	16.9 ± 1.4	147.5 ± 7.2	200.4 ± 47.8	145.8 ± 30.6	45.8 ± 7.6	36.3 ± 14.0	23.8 ± 10.6	5.2 ± 1.3	8.2 ± 0.6
2	14.5 ± 1.6	172.7 ± 18.0	192.0 ± 18.4	87.8 ± 22.4	57.8 ± 8.0	17.7 ± 10.7	11.8 ± 26.4	7.8 ± 1.4	12.6 ± 4.8
3	17.2 ± 1.6	196.2 ± 10.6	236.3 ± 35.4	67.5 ± 16.5	50.1 ± 8.7	17.4 ± 4.7	8.5 ± 0.8	10.5 ± 1.1	7.8 ± 1.2
Replicate	Adrenal Weight, Mg.								
1	43.9 ± 2.6	36.7 ± 2.9	38.1 ± 3.5	44.0 ± 5.1	46.2 ± 4.2	34.1 ± 2.2	39.5 ± 3.4	34.2 ± 3.5	32.9 ± 2.2
2	44.9 ± 3.5	35.2 ± 3.6	47.8 ± 4.0	44.2 ± 2.0	34.6 ± 2.2	33.7 ± 2.6	43.6 ± 3.4	46.3 ± 3.3	41.2 ± 1.8
3	48.8 ± 4.1	44.3 ± 2.4	48.1 ± 1.4	49.4 ± 5.9	46.9 ± 5.3	45.4 ± 3.0	48.9 ± 3.1	46.8 ± 2.6	49.8 ± 2.7
Replicate	Male Gonad Weight, Mg.								
1	77.9 ± 9.5	48.4 ± 2.8	67.3 ± 5.1	110.8 ± 8.7	102.1 ± 12.0	97.9 ± 8.9	72.3 ± 11.6	113.8 ± 15.8	126.9 ± 7.8
2	97.5 ± 10.3	69.6 ± 8.6	90.9 ± 8.7	71.4 ± 4.6	59.7 ± 1.1	73.4 ± 13.1	110.2 ± 28.1	89.2 ± 8.9	91.3 ± 14.5
3	67.3 ± 4.6	90.6 ± 8.9	107.5 ± 5.1	120.4 ± 23.0	73.9 ± 10.7	112.5 ± 21.2	130.4 ± 10.9	98.5 ± 5.3	102.5 ± 15.7
Replicate	Female Gonad Weight, Mg.								
1	74.3 ± 10.3	39.3 ± 4.5	64.6 ± 8.1	78.9 ± 8.5	71.7 ± 15.2	69.5 ± 5.9	70.5 ± 5.2	68.7 ± 4.7	70.9 ± 4.1
2	69.2 ± 0.0	48.1 ± 6.5	76.6 ± 11.2	68.8 ± 5.4	58.9 ± 3.5	67.1 ± 5.6	70.8 ± 5.9	73.2 ± 5.9	70.2 ± 5.6
3	58.7 ± 6.2	49.0 ± 4.2	87.0 ± 29.1	64.3 ± 10.1	67.8 ± 6.4	73.1 ± 5.4	71.9 ± 12.1	70.0 ± 6.7	82.8 ± 9.9
Replicate	Male Comb Weight, Mg.								
1	282.3 ± 50.5	22.1 ± 6.3	155.6 ± 35.1	236.3 ± 28.9	274.6 ± 46.8	368.0 ± 36.0	221.5 ± 44.3	282.4 ±116.1	551.5 ±184.5
2	286.4 ± 54.3	47.5 ± 4.0	225.9 ± 39.9	224.7 ± 11.5	172.9 ± 85.5	269.7 ± 70.3	280.0 ± 38.9	269.3 ± 67.3	406.2 ± 81.3
3	179.0 ± 37.9	48.4 ± 5.4	202.6 ± 32.7	337.5 ± 64.5	214.9 ± 51.3	406.3 ±157.0	491.1 ± 15.7	407.1 ± 66.3	354.8 ± 56.3
Replicate	Female Comb Weight, Mg.								
1	74.3 ± 13.8	39.3 ± 6.3	64.6 ± 10.8	78.9 ± 18.3	71.7 ± 21.3	69.5 ± 7.6	70.5 ± 10.4	68.7 ± 5.9	70.9 ± 6.3
2	69.2 ± 1.4	48.1 ± 1.3	76.6 ± 12.8	68.8 ± 13.6	58.9 ± 9.1	67.1 ± 5.6	70.8 ± 34.7	73.2 ± 12.3	70.2 ± 12.1
3	58.7 ± 6.4	49.0 ± 1.7	87.0 ± 8.7	64.3 ± 9.1	67.8 ± 6.8	73.1 ± 4.7	71.9 ± 7.7	70.0 ± 6.9	82.3 ± 7.6

TABLE II (Cont'd)

Replicate			Heart Weight, Gms.						
1	2.25 ± 0.10	1.20 ± 0.01	2.14 ± 0.20	2.03 ± 0.10	2.29 ± 0.10	1.77 ± 0.10	1.76 ± 0.20	2.01 ± 0.30	1.94 ± 0.10
2	2.55 ± 0.20	1.42 ± 0.10	1.85 ± 0.10	1.90 ± 0.10	1.60 ± 0.20	1.81 ± 0.10	1.76 ± 0.30	1.83 ± 0.30	1.78 ± 0.10
3	1.90 ± 0.10	1.49 ± 0.10	2.07 ± 0.10	1.89 ± 0.10	1.97 ± 0.10	1.78 ± 0.20	1.78 ± 0.10	1.51 ± 0.20	1.93 ± 0.10
Replicate			**Average Revolutions to Exhaust (with Range)**						
1	195(15-1005)	165(15- 945)	255(15-1035)	420(30-1185)	465(15-1380)	285(15-1245)	345(15-1200)	210(15- 735)	195(15- 855)
2	435(30- 975)	180(30- 495)	390(45- 885)	330(30- 915)	405(45-1035)	420(30-1860)	495(15-2925)	375(30-1035)	540(45-1680)
3	645(45-1905)	480(60-1455)	495(60-1440)	720(45-1575)	765(60-2100)	630(75-1725)	240(60- 525)	495(30-1650)	675(45-1800)
Pooled Mean	405(15-1905)	355(15-1455)	360(15-1440)	465 (30-1575)	540(15-2100)	435(15-1860)	375(15-2925)	405(15-1650)	465(15-1800)

TABLE III

Pooled Mean Values of Body Weight, Weight of Thyroid, Adrenal, Gonads, Comb, and Heart of Stressed and Unstressed New Hampshire Chicks on Normal Diet and on Diets Containing Thiouracil Plus Graded Levels of Protamone

	% Thiouracil									
	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Gms. Protamone/cwt									
	0.0	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
	Body Weight, Gms.									
Stress	329 ± 9.0	235 ± 6.4		313 ± 6.8	314 ± 7.7	283 ± 15.9	285 ± 7.8	295 ± 6.5	285 ± 5.8	303 ± 6.7
No Stress	316 ± 5.1	213 ± 11.7	285 ± 6.7	301 ± 6.6		301 ± 7.0		299 ± 5.7		
	Thyroid Weight, Mg.									
Stress	16.2 ± 0.9**	170.3 ± 22.3		207.6 ± 19.7	105.3 ± 15.4	36.2 ± 4.7	24.2 ± 5.5	15.1 ± 4.1	7.5 ± 0.8	9.2 ± 1.6
No Stress	20.5 ± 1.1**	182.0 ± 18.8	208.6 ± 17.3	152.8 ± 13.0		36.2 ± 9.7		12.7 ± 1.7		
	Adrenal Weight, Mg.									
Stress	45.9 ± 1.3*	38.3 ± 1.5**		42.7 ± 2.5**	45.7 ± 2.2	39.7 ± 2.8**	39.7 ± 1.7	43.3 ± 2.0**	42.4 ± 3.3	42.8 ± 1.7
No Stress	28.9 ± 1.0**	25.7 ± 0.9**	28.0 ± 1.1	30.3 ± 1.2**		27.5 ± 1.1**		29.0 ± 1.8**		
	Male Gonad Weight, Mg.									
Stress	81.0 ± 5.4	69.5 ± 5.8		87.4 ± 5.5	101.6 ± 9.3	86.7 ± 8.7	88.5 ± 9.8	96.1 ± 8.0	90.5 ± 6.0	104.3 ± 8.8
No Stress	68.3 ± 14.9	66.0 ± 6.7	77.1 ± 4.9	82.9 ± 4.4		73.4 ± 3.7		78.7 ± 20.7		
	Female Gonad Weight, Mg.									
Stress	58.0 ± 5.2	43.9 ± 5.3		75.1 ± 5.4**	71.1 ± 4.9	64.1 ± 3.8	70.0 ± 3.1	71.2 ± 4.7	70.3 ± 3.1	75.9 ± 3.9
No Stress	61.8 ± 2.9	37.5 ± 1.7	51.5 ± 3.0	52.7 ± 2.0**		61.7 ± 2.8		62.6 ± 7.6		
	Male Comb Weight, Mg.									
Stress	227.8 ± 27.7	38.2 ± 3.3		187.2 ± 22.1	246.6 ± 25.5	239.8 ± 30.8	321.7 ± 25.9	300.1 ± 43.2	305.6 ± 45.6	392.6 ± 64.6
No Stress	242.6 ± 20.2	35.8 ± 6.2	140.4 ± 12.8	176.2 ± 15.3		221.6 ± 31.2		209.6 ± 25.3		
	Female Comb Weight, Mg.									
Stress	73.5 ± 7.5	26.6 ± 3.5		72.4 ± 5.8**	85.5 ± 9.9	68.5 ± 6.4	64.4 ± 4.1	69.2 ± 5.2	68.8 ± 9.0	67.9 ± 5.4
No Stress	57.2 ± 3.5	21.8 ± 1.3	38.2 ± 2.4	45.7 ± 2.7**		62.0 ± 4.3		57.2 ± 9.7		
	Heart Weight, Gms.									
Stress	2.16 ± 0.09	1.36 ± 0.06**		2.01 ± 0.07*	1.95 ± 0.08	1.93 ± 0.08	1.79 ± 0.07	1.85 ± 0.04	1.80 ± 0.10	1.89 ± 0.07
No Stress	2.01 ± 0.03	1.17 ± 0.02**		1.80 ± 0.03*	1.94 ± 0.002	2.02 ± 0.06	1.91 ± 0.04	1.89 ± 0.03	2.09 ± 0.06	2.03 ± 0.04

*Difference between these means significant at 5% level (t-test).

**Difference between these means significant at 1% level (t-test).

TABLE IV

Pooled Mean Values of Body Weight, Thyroid Weight, and Adrenal Weight of New Hampshire Chicks on Normal Diet and on Diets Containing Thiouracil Plus Graded Levels of Protamone. Data Analyzed for the Two Sexes Separately

	% Thiouracil					
	0.0	0.2	0.2	0.2	0.2	0.2
	Gms. Protamone/cwt					
	0.0	0.0	0.5	1.0	2.0	3.0
	Average Body Weight, Gms.					
Males	338±12.8	216± 8.7	295±10.6	314± 9.6	306±10.8	310±8.1
Females	311± 8.9	200± 7.5	278± 8.1	291±33.4	296± 9.0	293±8.0
	Average Thyroid Weight, Mg.					
Males	19.1± 1.0	178.1±26.3	193.1±28.1	148.7±18.2	24.5± 1.4	16.9±1.5
Females	21.5± 1.7	178.2±27.4	221.5±28.5	158.8±19.4	49.6±20.2	14.5±3.1
	Average Adrenal Weight, Mg.					
Males	33.0± 1.7*	26.4± 1.7	27.4± 1.9	33.0± 1.7*	29.4± 1.4	35.4±2.3
Females	26.0± 1.1**	23.9± 1.3	24.9± 1.4	27.8± 1.4*	25.4± 1.7	25.4±1.7

*Difference between these means significant at 5% level (t-test).

**Difference between these means significant at 1% level (t-test).

TABLE V

Pooled Mean Values of Body Weight, Weight of Thyroid, Adrenal and Heart, and Exhaustion Time of New Hampshire Chicks Exposed to Stress While on Normal Diet, and on Diet Containing Thiouracil Plus Graded Levels of Protamone. Data Analyzed for the Two Sexes Separately

	% Thiouracil								
	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Gms. Protamone/cwt								
	0.0	0.0	1.0	1.5	2.0	2.5	3.0	3.5	4.0
	Average Body Weight, Gms.								
Males	336 ± 11.9	229 ± 8.4	317 ± 9.5	326 ± 13.5	314 ± 15.3	304 ± 10.9	301 ± 9.6	295 ± 7.6	309 ± 12.3
Females	323 ± 12.7	246 ± 8.7	315 ± 10.0	305 ± 8.1	279 ± 10.8	275 ± 6.2	289 ± 8.8	278 ± 8.0	298 ± 6.6
	Average Thyroid Weight, Mg.								
Males	15.4 ± 1.1	140.8 ± 20.6	185.6 ± 25.7	102.1 ± 16.2	46.0 ± 7.0	53.0 ± 16.7	19.6 ± 7.7	9.5 ± 1.4*	8.4 ± 1.0
Females	21.1 ± 3.6	229.4 ± 48.8	241.8 ± 32.4	104.3 ± 26.2	31.7 ± 6.0	23.2 ± 6.0	10.2 ± 1.9	6.5 ± 0.9*	10.6 ± 3.1
	Average Adrenal Weight, Mg.								
Males	48.6 ± 2.0**	41.6 ± 2.0*	48.0 ± 2.6*	50.9 ± 3.6*	46.3 ± 3.7	45.2 ± 2.3*	47.4 ± 1.7*	45.5 ± 2.7	47.6 ± 2.0**
Females	39.9 ± 1.6**	33.0 ± 3.4*	38.0 ± 2.2*	40.8 ± 1.7*	38.0 ± 3.0	36.0 ± 2.0*	38.9 ± 3.4*	40.3 ± 3.0	38.6 ± 2.1**
	Average Heart Weight, Gms.								
Males	2.28 ± 0.04**	1.39 ± 0.08	2.07 ± 0.10	2.07 ± 0.14	2.20 ± 0.14**	1.91 ± 0.11	1.90 ± 0.07	2.04 ± 0.22	2.06 ± 0.10
Females	1.87 ± 0.10**	1.31 ± 0.08	1.89 ± 0.05	1.80 ± 0.05	1.76 ± 0.08**	1.71 ± 0.10	1.75 ± 0.05	1.64 ± 0.08	1.77 ± 0.09
	Average Revolutions to Exhaust, and Range								
Males	470(15-2070)	281(15-1455)	435(15-1440)	539(45-1305)	605(15-1740)	559(15-1860)	477(30-1530)	432(15-1035)	633(15-1800)
Females	237(15-1440)	215(15-1140)	209(15- 825)	371(30-1590)	512(30-2100)	366(15-1575)	257(15-1440)	339(30-1650)	282(30-1300)

*Difference between these means significant at 5% level (t-test).

**Difference between these means significant at 1% level (t-test).

TABLE VI

Mean Values of Body Weight, Weight of Thyroid, Adrenal, Gonads, Comb, and Heart, and Exhaustion Time of Stressed and Unstressed New Hampshire Chicks Injected with Small Amounts of Androgen

Treatment			
0.07 Mg. Androgen	No Treatment	0.07 Mg. Androgen Plus Exercise	Exercise
	Average Body Weight, Gms.		
309 ± 8.9	291 ± 4.3	301 ± 10.3	287 ± 11.0
	Average Thyroid Weight, Mg.		
13.7 ± 1.2	17.5 ± 0.9	17.1 ± 1.3	13.4 ± 1.2
	Average Adrenal Weight, Mg.		
35.8 ± 2.0	40.8 ± 2.1	46.3 ± 2.0	45.0 ± 2.8
	Average Male Gonad Weight, Mg.		
67.0 ± 18.0	76.7 ± 5.0	58.1 ± 6.1	79.5 ± 5.2
	Average Female Gonad Weight, Mg.		
59.7 ± 4.2	66.2 ± 4.4	58.2 ± 7.9	56.1 ± 2.2
	Average Male Comb Weight, Mg.		
263.1 ± 31.4	203.5 ± 35.3	185.2 ± 21.2	151.0 ± 15.2
	Average Female Comb Weight, Mg.		
103.6 ± 9.9	76.8 ± 12.3	97.1 ± 1.1	56.6 ± 6.2
	Average Heart Weight, Mg.		
1.71 ± 0.05	1.63 ± 0.05	1.89 ± 0.06	1.81 ± 0.07
	Average Revolutions to Exhaust, and Range		
	990(120-3510)		885(45-3195)

TABLE VII

Mean Values of Body Weight, Weight of Thyroid, Adrenal, Gonads, Comb, and Heart, and Exhaustion Time of Stressed and Unstressed New Hampshire Chicks Injected with Large Amounts of Androgen, Estrogen, and Gonadotropin

Treatment									
		0.7 Mg. Androgen/Bird		1.4 Mg. Androgen/Bird		0.7 Mg. Estrogen/Bird		70 Units Gonadotropin/Bird	
Stress	No Stress	Stress	No Stress	Stress	No Stress	Stress	No Stress	Stress	No Stress
				Average Body Weight, Gms.					
249 ± 18.9	273 ± 10.0	252 ± 11.1*	292 ± 9.9*	266 ± 11.2	301 ± 14.1	272 ± 7.0*	303 ± 12.5*	235 ± 17.8	264 ± 7.9
				Average Thyroid Weight, Mg.					
16.1 ± 1.8	16.0 ± 1.6	10.8 ± 2.4*	16.8 ± 1.7*	12.7 ± 1.2*	15.7 ± 1.2	16.3 ± 1.4	18.1 ± 2.5	12.7 ± 2.0	15.1 ± 1.8
				Average Adrenal Weight, Mg.					
44.0 ± 3.8	37.4 ± 1.9	40.9 ± 3.3*	33.5 ± 1.3*	46.6 ± 2.4**	36.8 ± 2.3**	45.7 ± 2.8	44.5 ± 1.9	39.1 ± 1.6	38.0 ± 1.6
				Average Male Gonad Weight, Mg.					
68.2 ± 9.4	114.5 ± 24.3	46.9 ± 40.2	45.8 ± 0.0	48.4 ± 5.0	47.3 ± 5.6	57.8 ± 3.1	48.6 ± 10.3	79.9 ± 11.7	73.6 ± 11.9
				Average Female Gonad Weight, Mg.					
53.2 ± 6.0	59.7 ± 4.4	39.3 ± 3.4*	49.2 ± 3.4*	42.0 ± 5.8	42.1 ± 6.2	49.7 ± 3.3	47.3 ± 6.4	50.1 ± 2.9	54.2 ± 4.8
				Average Male Comb Weight, Mg.					
185.9 ± 8.6**	448.1 ± 60.1**	716.2 ±127.0	965.2 ±515.9	820.0 ± 52.0	918.4 ±132.2	96.9 ± 28.8	128.3 ± 13.0	208.7 ± 25.6	152.2 ± 38.8
				Average Female Comb Weight, Mg.					
-----	71.2 ± 5.4	318.4 ± 17.3**	607.7 ± 68.9**	578.3 ±107.8	551.0 ±181.0	63.4 ± 8.4	77.1 ± 7.3	61.6 ± 10.2	77.2 ± 11.9
				Average Heart Weight, Gms.					
1.78 ± 0.09	1.79 ± 0.07	1.88 ± 0.10	1.65 ± 0.09	1.83 ± 0.08	1.84 ± 0.09	1.80 ± 0.06	1.91 ± 0.09	1.53 ± 0.10	1.62 ± 0.07
				Average Revolutions to Exhaust, and Range					
900(195-2080)		1168(520-2190)		1308(345-2370)		1034(255-2085)		1403(210-2640)	

*Difference between stress and no-stress means significant at 5% level (t-test).

**Difference between stress and no-stress means significant at 1% level (t-test).

TABLE VII

Mean Values of Body Weight, Weight of Thyroid, Adrenal, Heart, and [illegible]tion Time of Stressed and Unstressed New Hampshire Chicks Injected with Large Amounts of Androgen, Estrogen, and Co[illegible]opin. Data Analysed for the two Sexes Separately

	Treatme[illegible]											
			0.7 Mg. Androgen/Bird		1.4 Mg. [illegible]en/Bird		0.7 Mg. Estrogen/Bird		70 Units Gonadotropin/Bird	
	Stress	No Stress	Stress	No Stress	Stress	No Stress	Stress	No Stress	Stress	No Stress
					Average Body We[illegible] Gms.					
Males	263 ± 43.4	274 ± 15.2	278 ± 9.2**	307 ± 1.6	282 ± 18[illegible]	308 ± 22.4	275 ± 16.0	299 ± 3.6	275 ± 28.4*	267 ± 14.9
Females	239 ± 18.2	272 ± 17.7	212 ± 2.4**	288 ± 12.0	249 ± 9[illegible]	291 ± 15.3	272 ± 6.6	305 ± 11.2	209 ± 16.5*	262 ± 10.3
					Average Thyroid [illegible]. Mg.					
Males	15.9 ± 1.0	12.2 ± 0.7	13.8 ± 3.[illegible]	16.4 ± 0.9	11.2 ± 1[illegible]	[illegible].3 ± 1.4	15.0 ± 3.6	12.5 ± 1.7*	16.1 ± 4.2	17.5 ± 2.7
Females	16.2 ± 3.0	21.7 ± 0.5	5.9 ± 2.0*	16.9 ± 2.2	14.3 ± 1[illegible]	[illegible].8 ± 1.8	17.2 ± 0.9	21.9 ± 3.2*	10.5 ± 1.5	14.1 ± 2.3
					Average Adrenal Weight, Mg.					
Males	52.4 ± 3.4*	38.2 ± 2.6	43.7 ± 4.2	38.6 ± 0.2**	40.2 ± 4.0	36.7 ± 2.9	53.4 ± 2.8*	43.9 ± 2.6	42.9 ± 1.3*	42.5 ± 2.8*
Females	38.4 ± 4.7*	36.3 ± 3.3	36.8 ± 4.9	32.2 ± 1.2**	44.9 ± 4.0	37.0 ± 4.4	40.7 ± 2.8*	44.9 ± 2.8	36.7 ± 1.9*	36.1 ± 2.0*
					Average Heart Weight, Gms.					
Males	1.80 ± 0.20	1.86 ± 0.09	2.04 ± 0.10*	1.68 ± 0.20	2.00 ± 0.09**	1.84 ± 0.10	1.93 ± 0.10	1.95 ± 0.10	1.84 ± 0.10**	1.68 ± 0.10
Females	1.72 ± 0.10	1.67 ± 0.10	1.68 ± 0.10*	1.57 ± 0.07	1.66 ± 0.08**	1.78 ± 0.10	1.71 ± 0.08	1.89 ± 0.10	1.55 ± 0.10**	1.59 ± 0.09
					Average Revolutions to Exhaust, and Range					
Males	1038 (195-2080)		1056 (520-2190)		1426 (675-2125)		1135 (560-1970)		1077 (750-2640)	
Females	918 (200-1840)		1351 (1060-1900)		1286 (345-2370)		966 (255-2085)		1220 (210-2300)	

*Difference between these male and female means significant at 5% level (t-test).

**Difference between these male and female means significant at 1% level (t-test).

CHART 1

CHART 1: Pooled Means of Body Weights of Stressed and Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

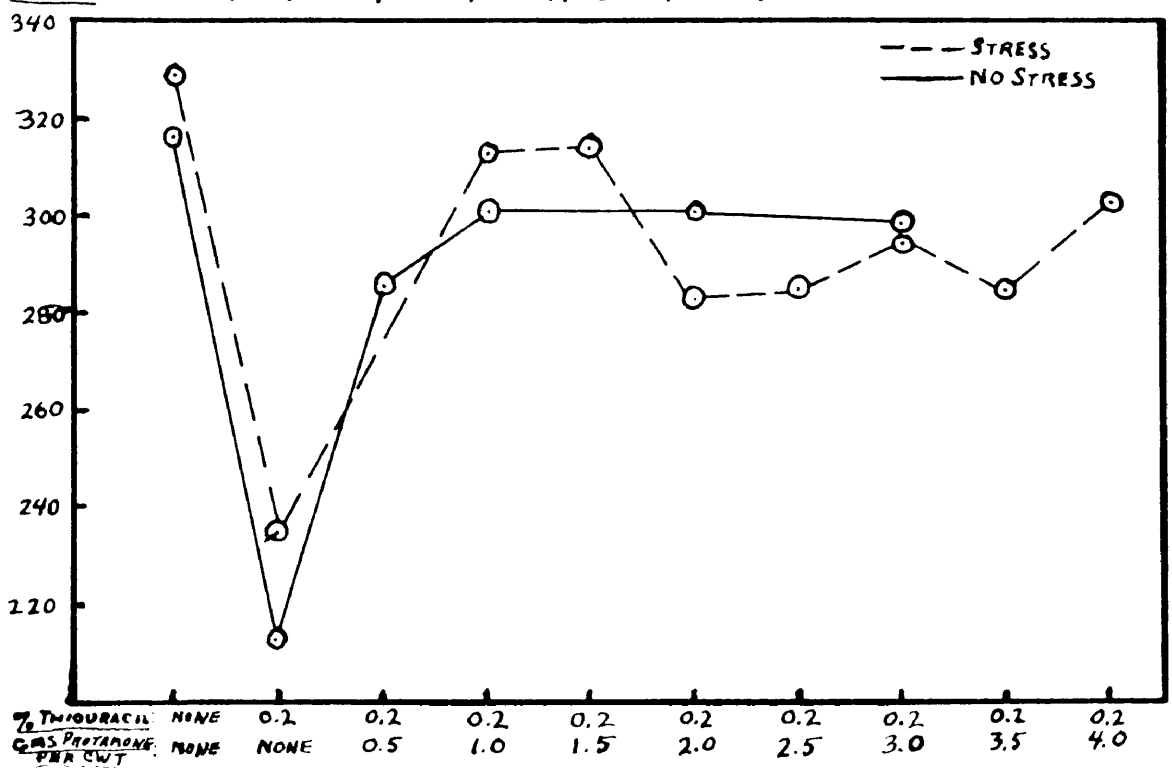


CHART 2: Pooled Means of Heart Weights of Stressed and Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

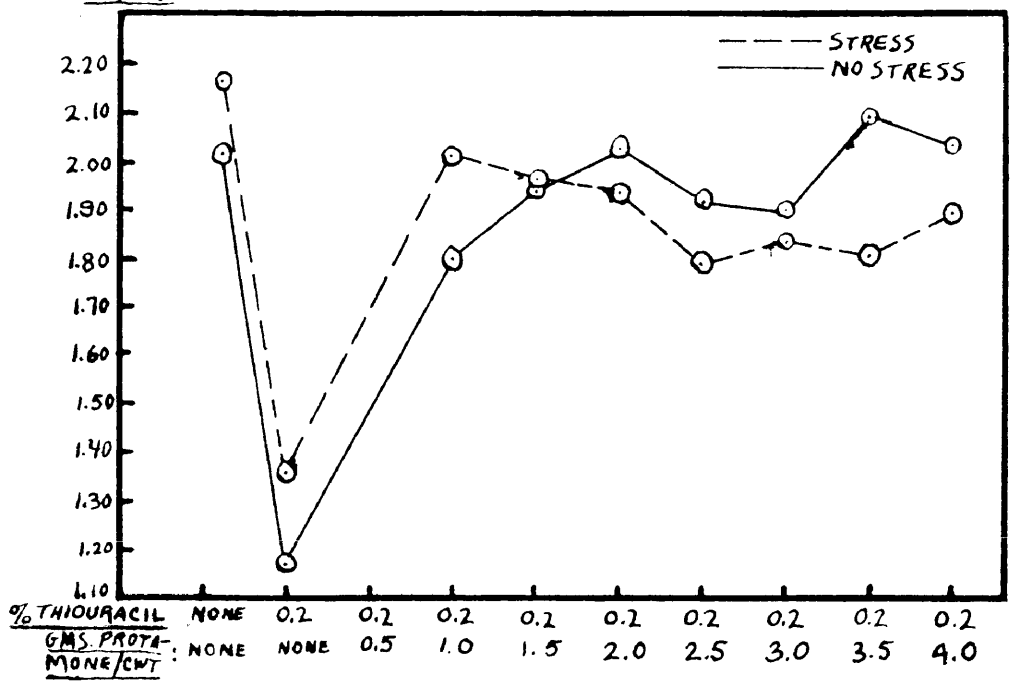


CHART 3: Pooled Means of Thyroid Weights of Stressed and Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

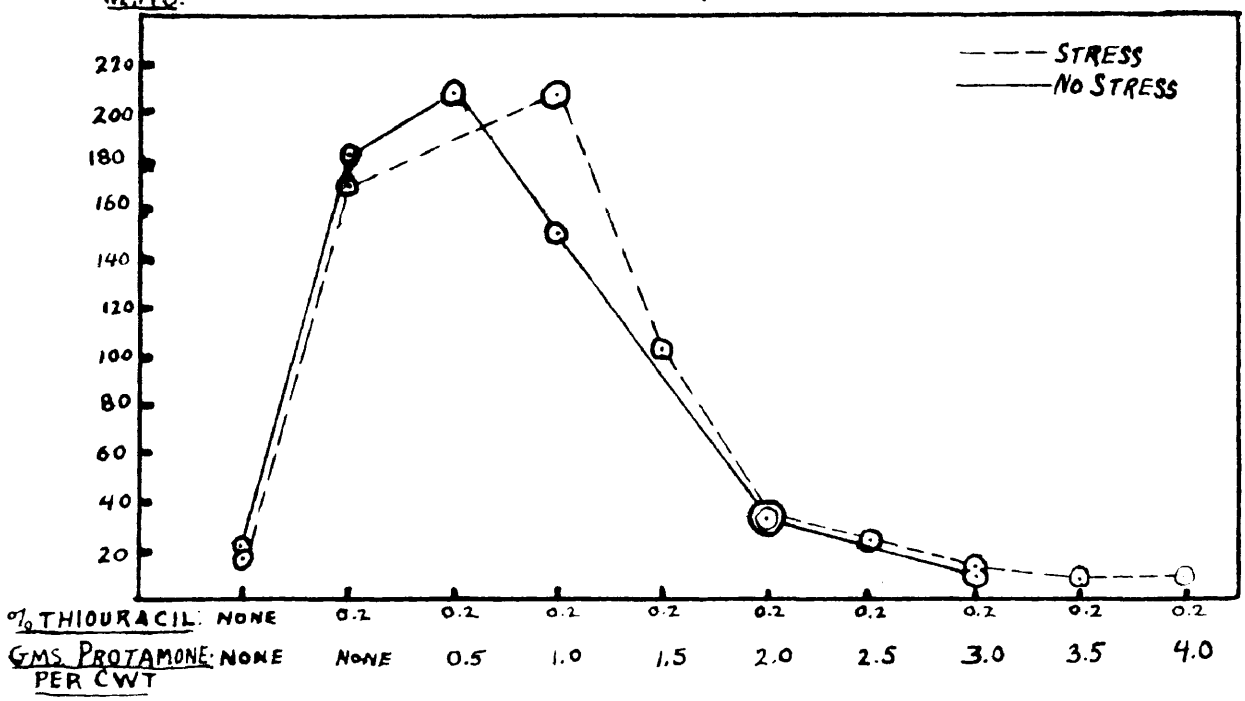


CHART 4: Pooled Means of Metabolic Rates of Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

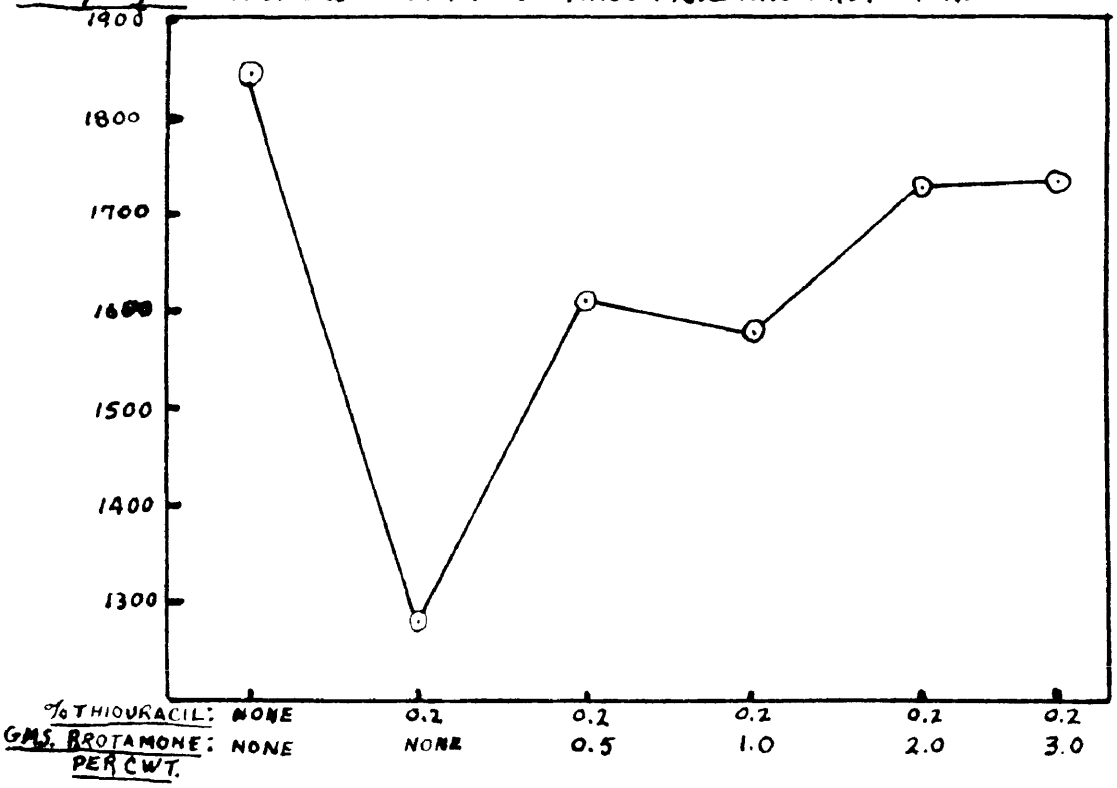


CHART 5: Pooled Means of Adrenal Weights of Stressed and Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

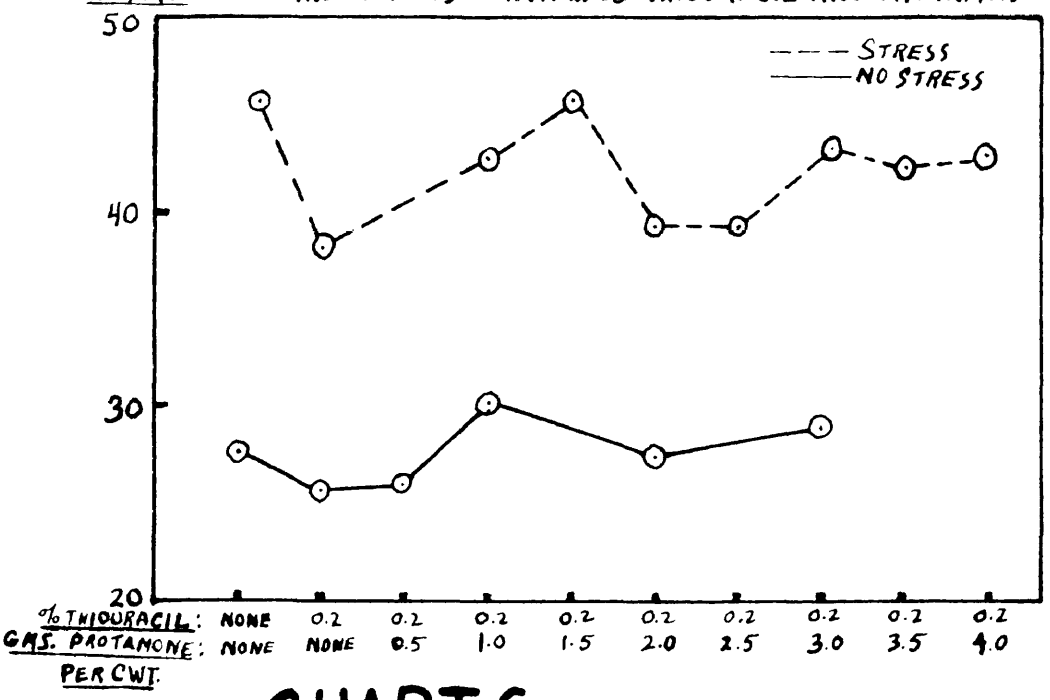


CHART 6: Pooled Means of Exercise Times of Stressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

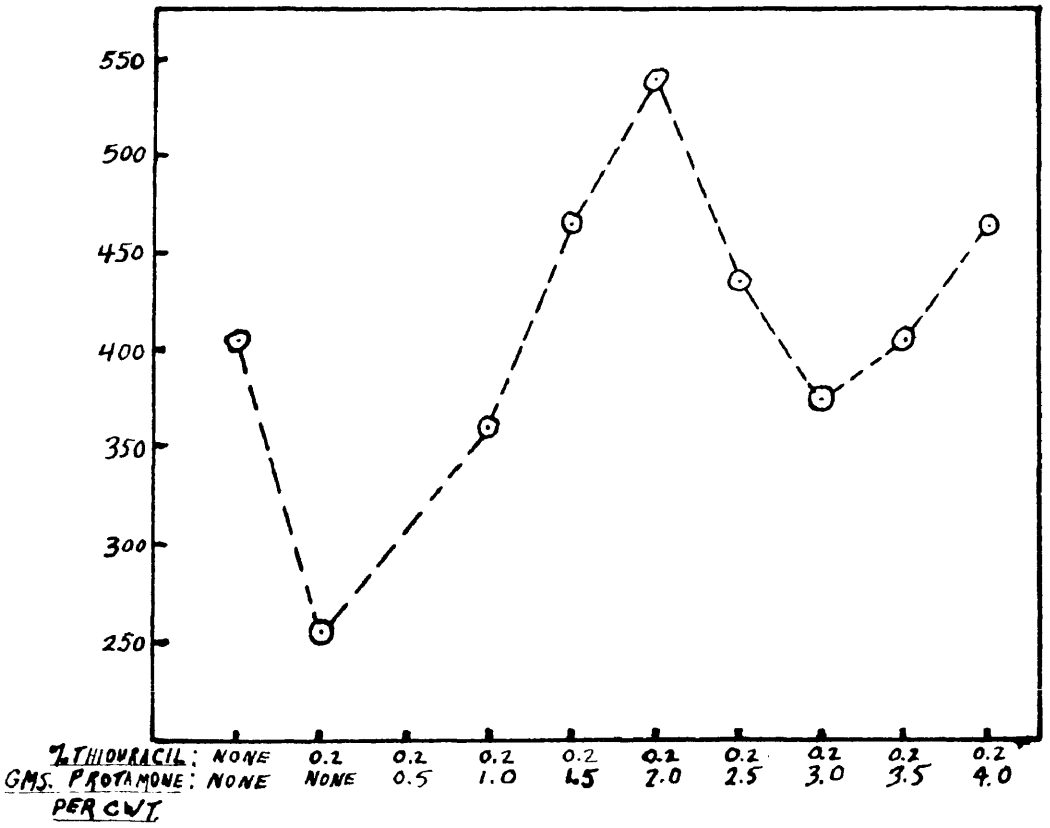


CHART 7: Pooled Means of Male Comb Weights of Stressed and Unstressed Chicks Fed Normal Ration and Ration Containing Thiouracil and Protamone.

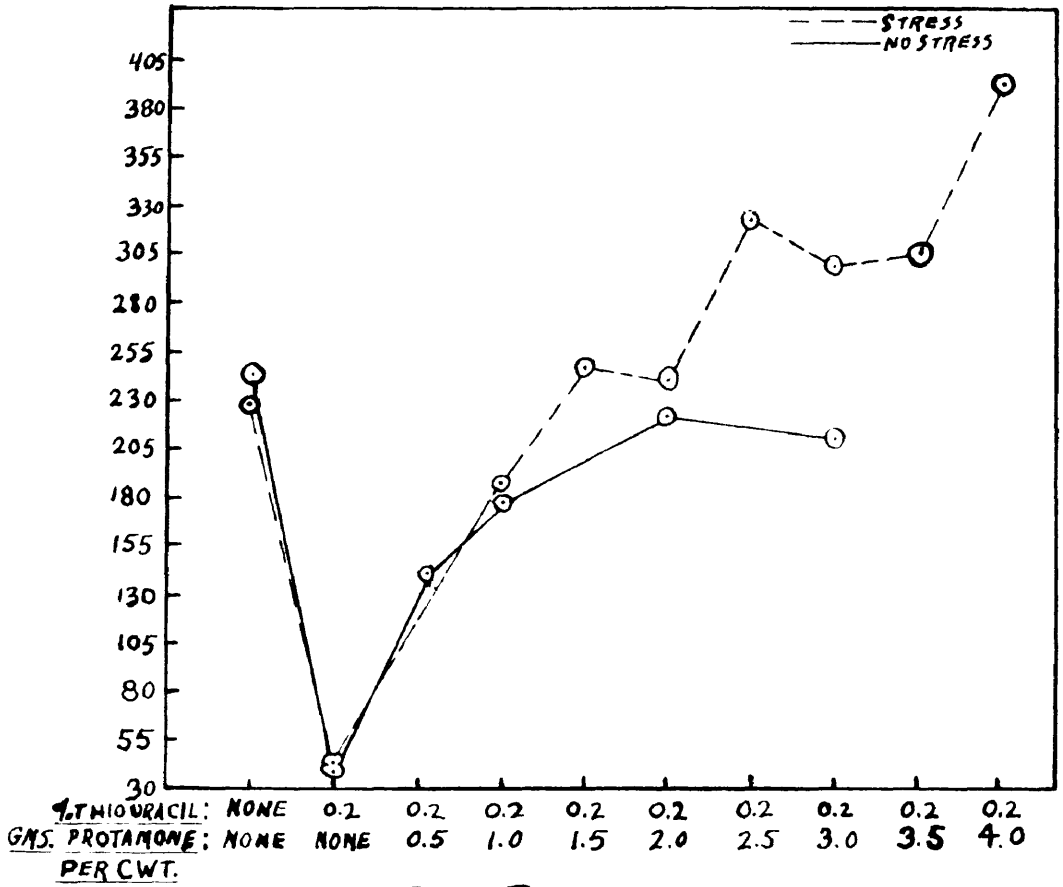


CHART 8: Pooled Means of Male Gonad Weights of Stressed and Unstressed Chicks Fed Normal Ration and Ration Containing Thiouracil and Protamone.

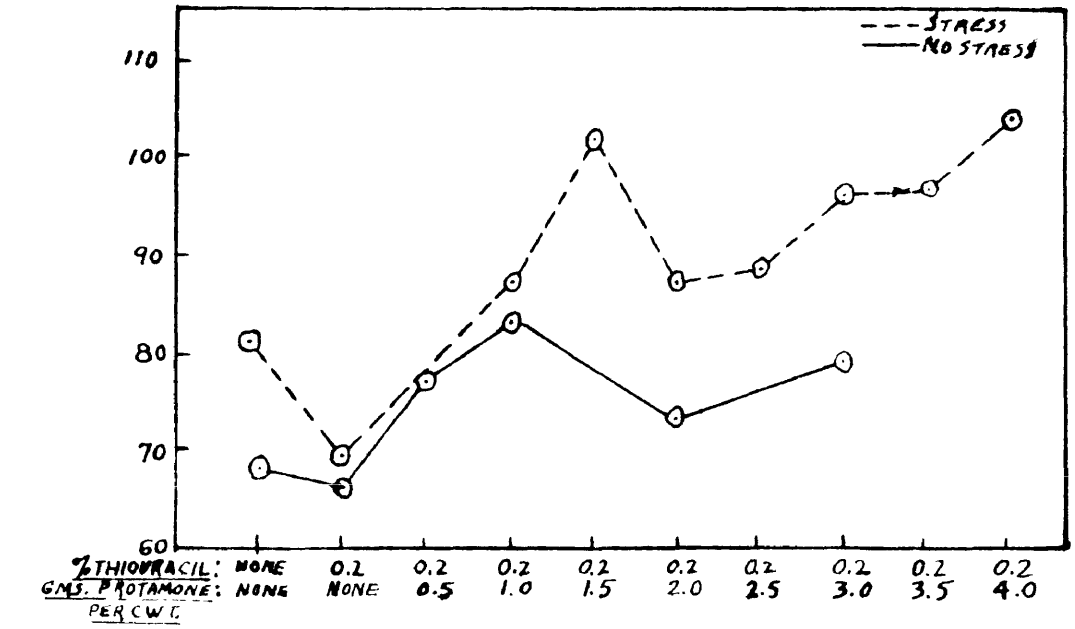


CHART 9: Pooled Means of Female Comb Weights of Stressed and Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone

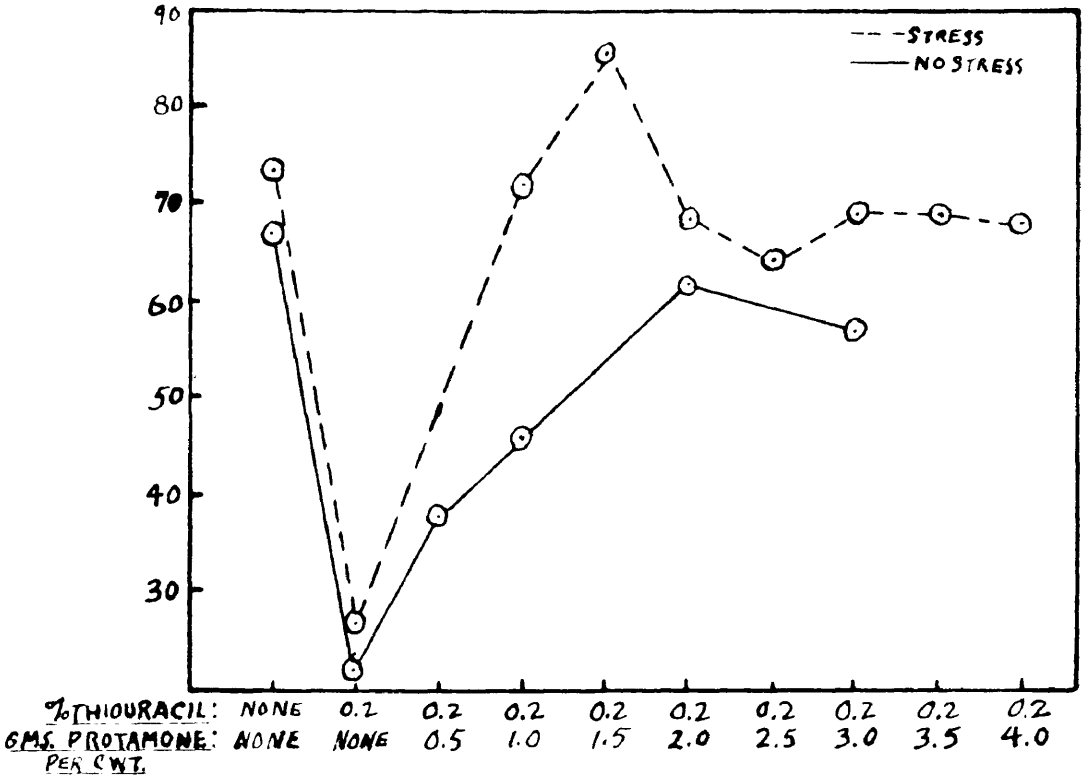


CHART 10: Pooled Means of Female Gonad Weights of Stressed and Unstressed Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.

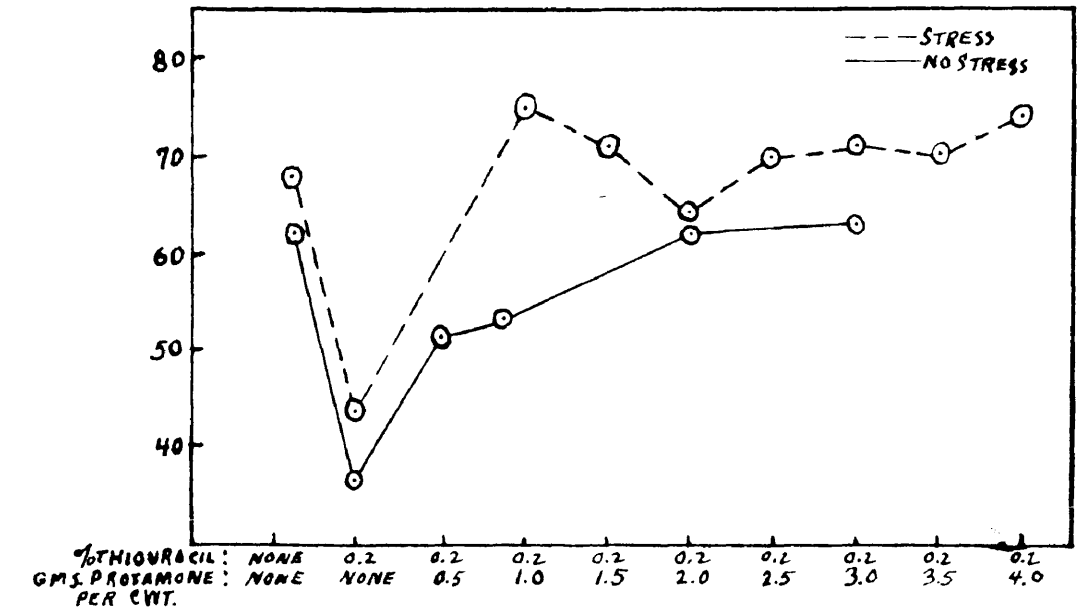


CHART 11: Mean Body Weights of Stressed and Unstressed Chicks Injected With Androgen, Estrogen, and Gonadotropin.

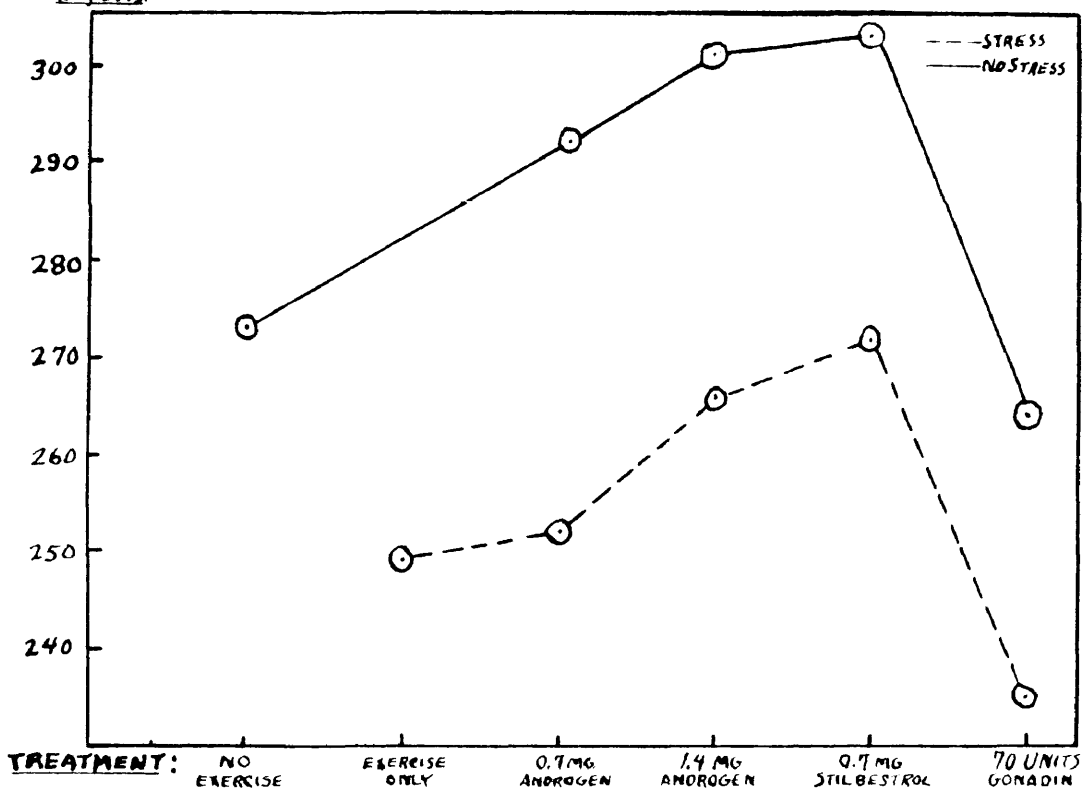


CHART 12: Mean Thyroid Weights of Stressed and Unstressed Chicks Injected With Androgen, Estrogen, and Gonadotropin.

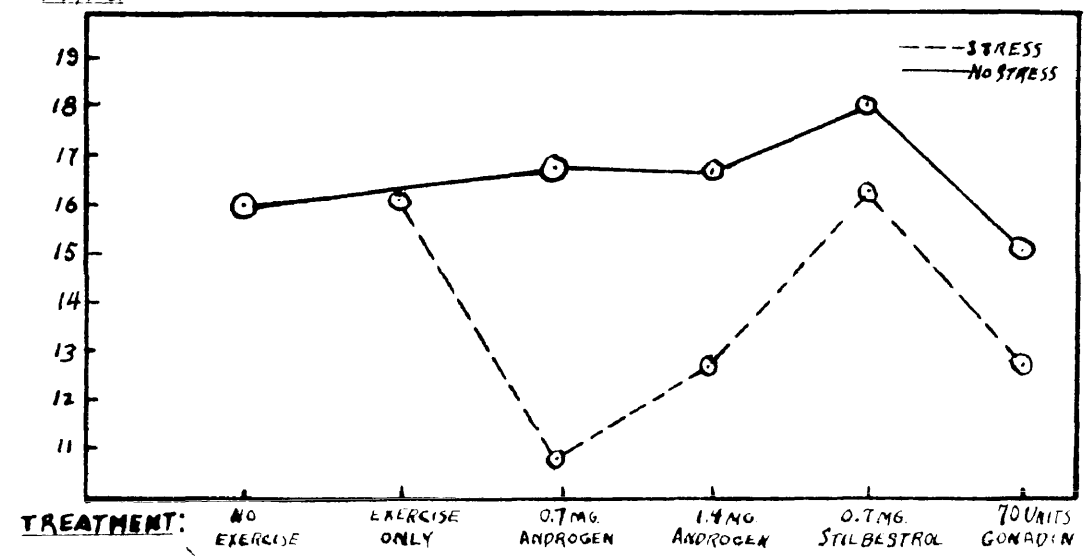


CHART 13: MEAN ADRENAL WEIGHTS OF STRESSED AND UNSTRESSED CHICKS INJECTED WITH ANDROGEN, ESTROGEN, AND GONADOTROPIN.

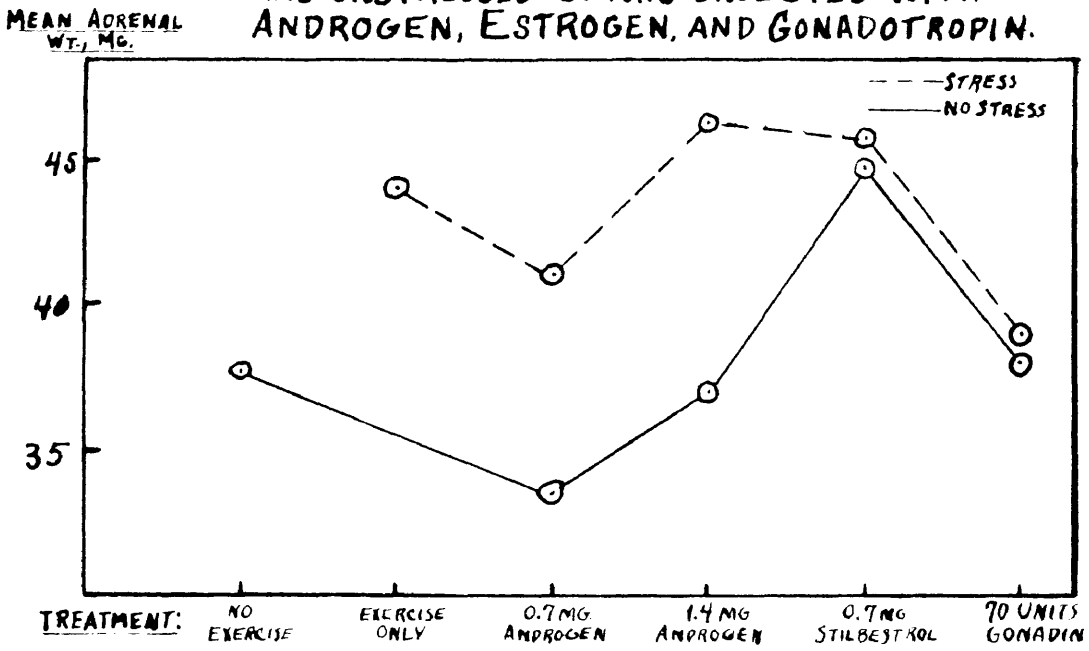


CHART 14: MEAN EXHAUSTION TIMES OF STRESSED CHICKS INJECTED WITH ANDROGEN, ESTROGEN, AND GONADOTROPIN.

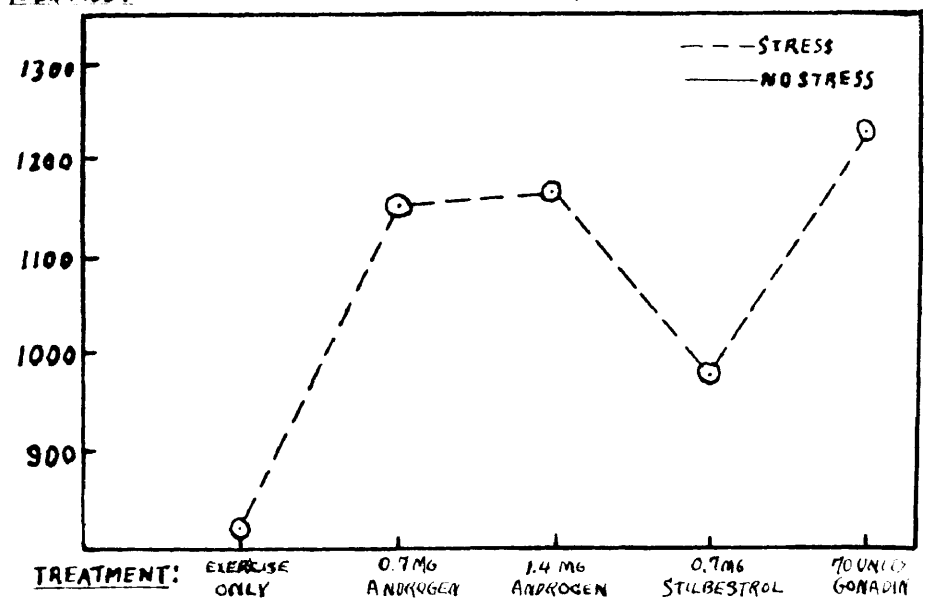


CHART 15: Mean Male Gonad Weights of Stressed and Unstressed Chicks Injected With Androgen, Estrogen, and Gonadotropin

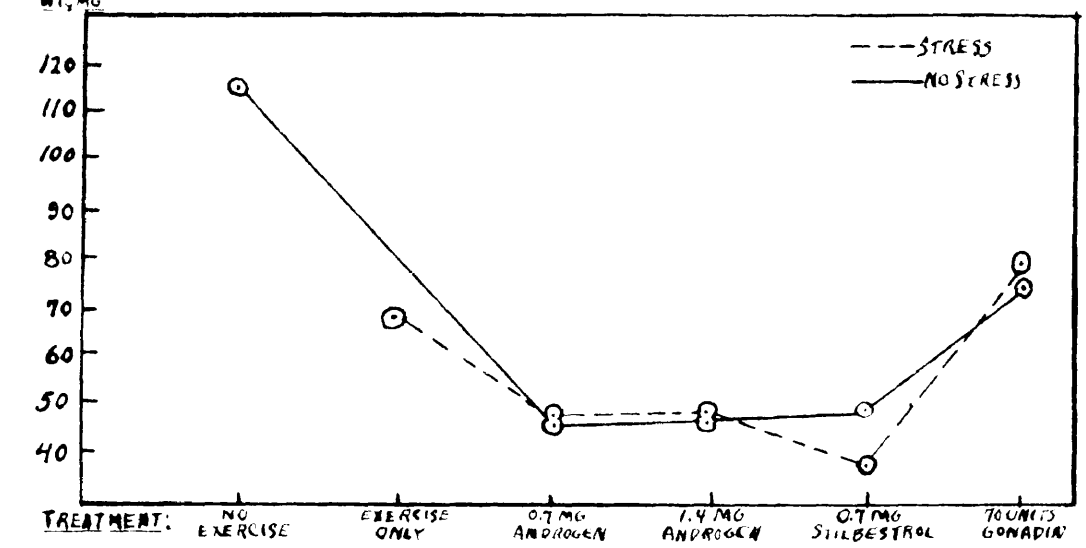


CHART 16: Mean Male Comb Weights of Stressed and Unstressed Chicks Injected With Androgen, Estrogen, and Gonadotropin.

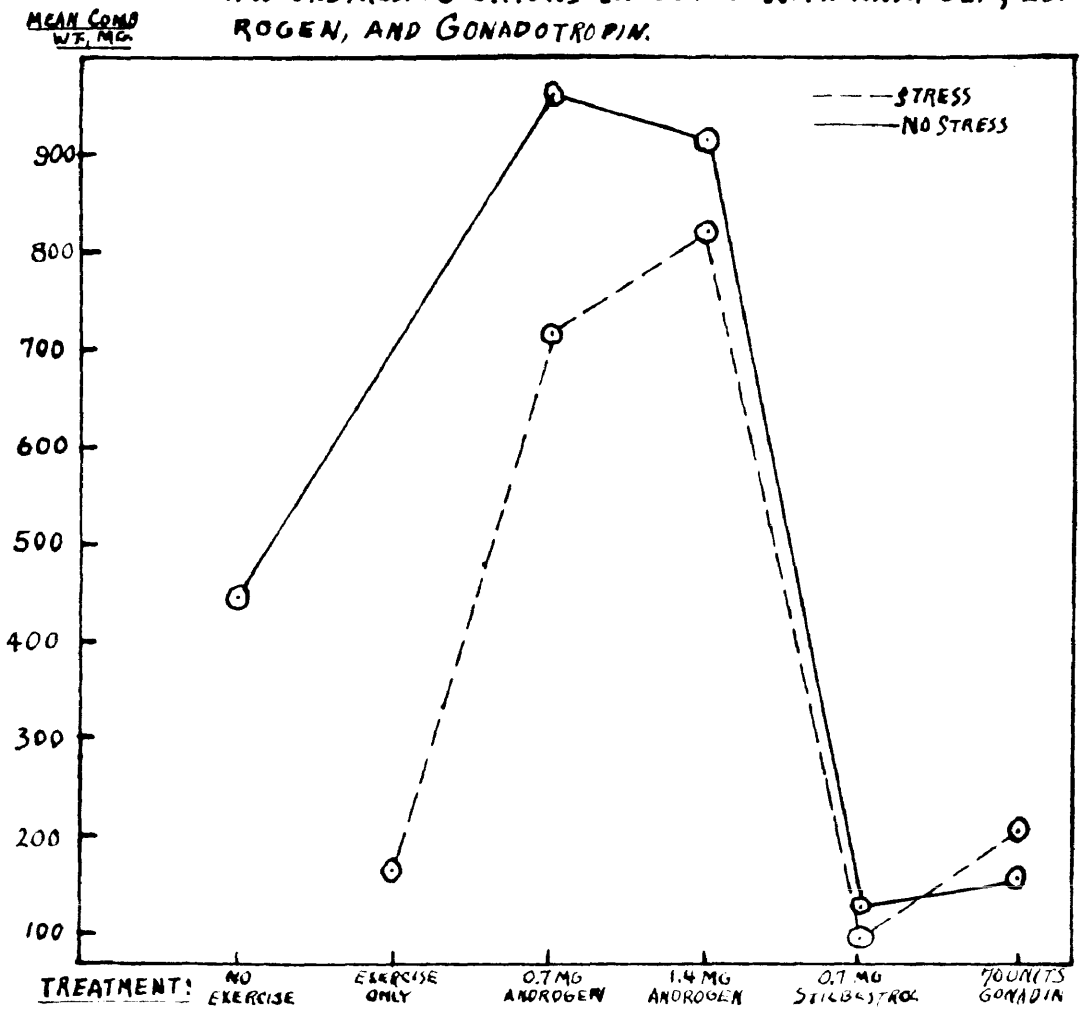


CHART 17: MEAN FEMALE GONAD WEIGHTS OF STRESSED AND UNSTRESSED CHICKS INJECTED WITH ANDROGEN, ESTROGEN, AND GONADOTROPIN.

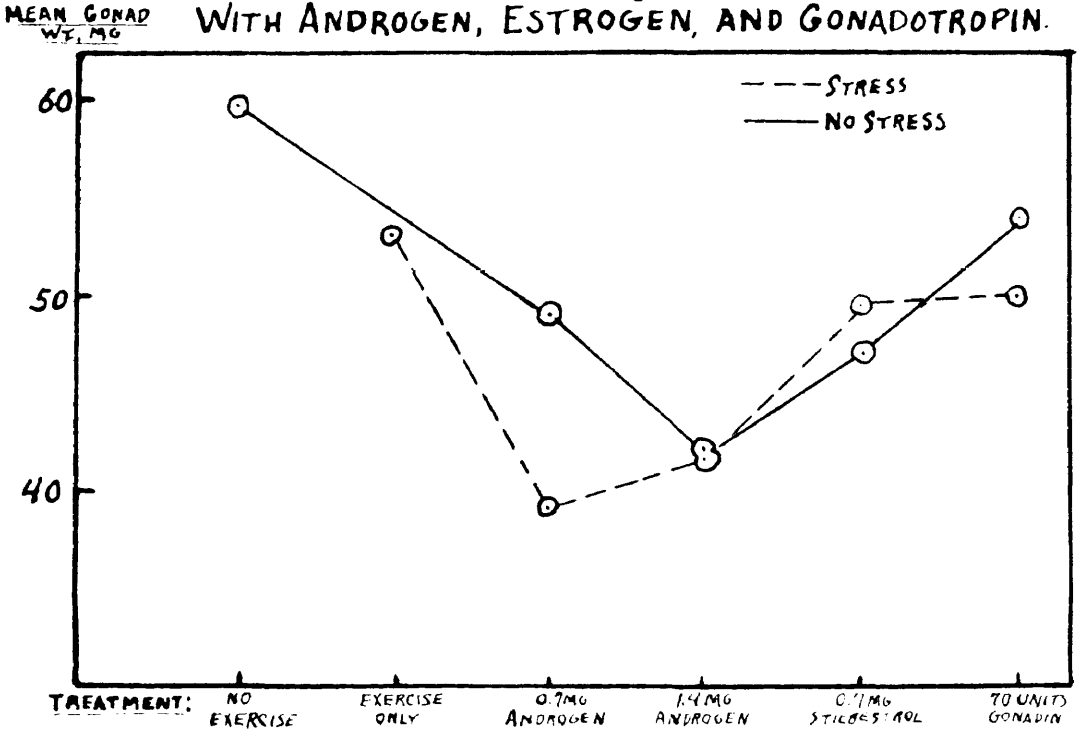


CHART 18: MEAN FEMALE COMB WEIGHTS OF STRESSED AND UNSTRESSED CHICKS INJECTED WITH ANDROGEN, ESTROGEN, AND GONADOTROPIN.

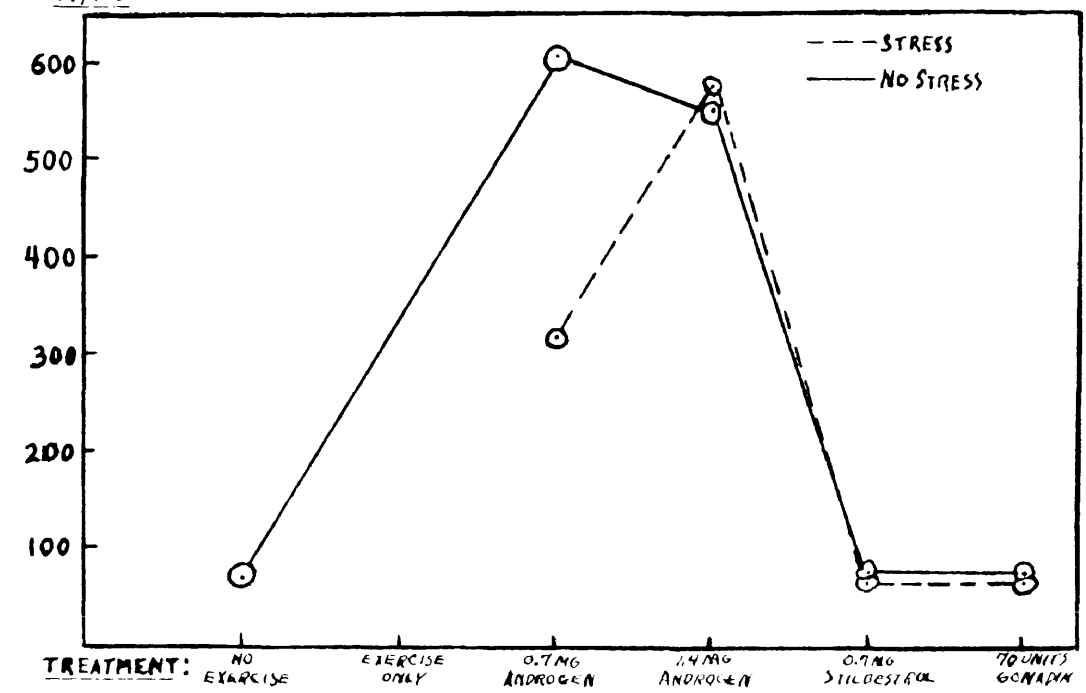


CHART 19: MEAN HEART WEIGHTS OF STRESSED AND UNSTRESSED CHICKS INJECTED WITH ANDROGEN, ESTROGEN, AND GONADOTROPIN.

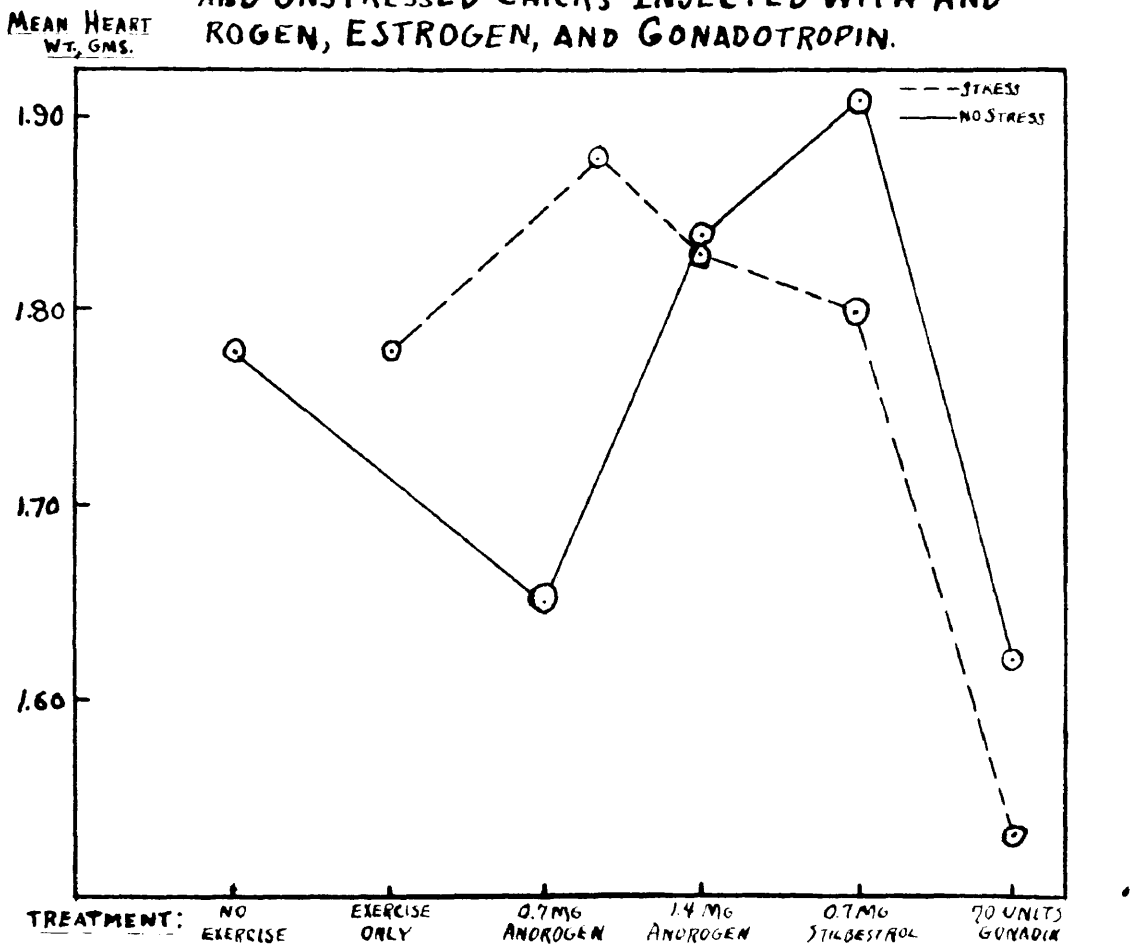
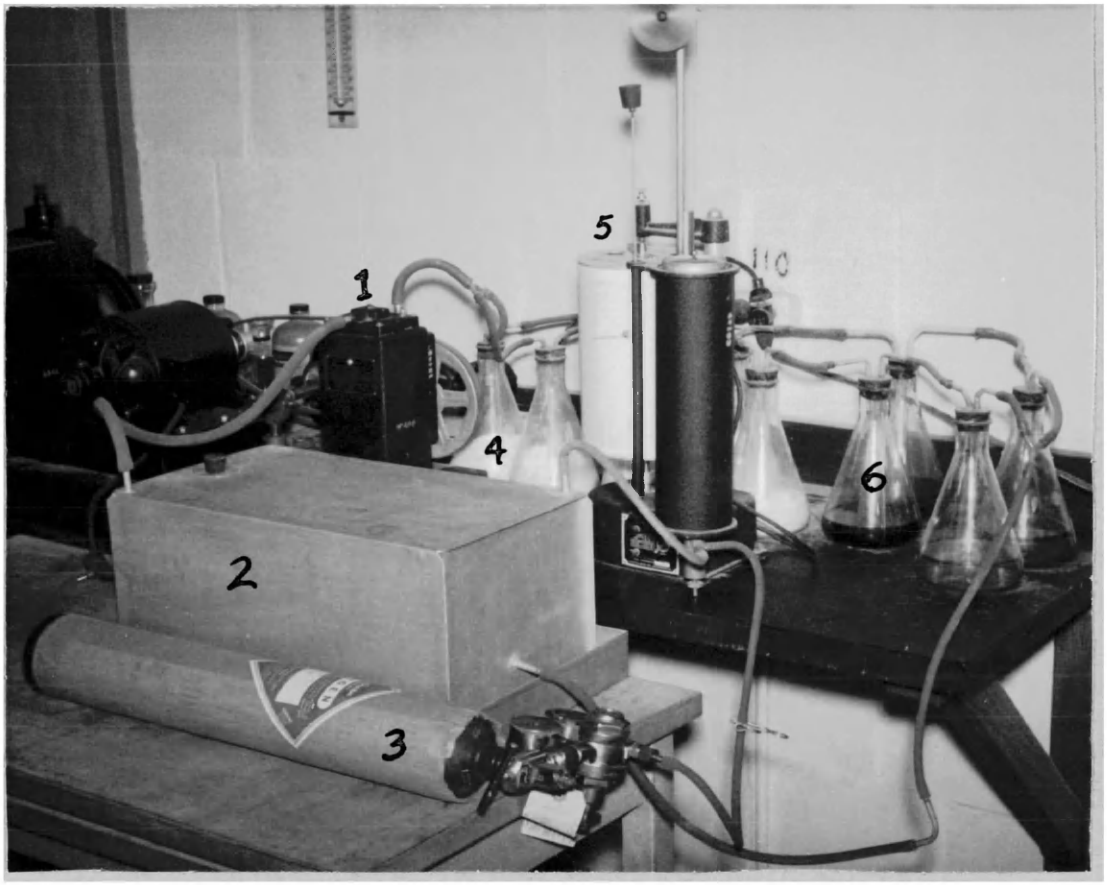


PLATE 1

Apparatus Used to Measure Metabolic Rate of Chicks Fed Normal Ration and Rations Containing Thiouracil and Protamone.



1 - Air Pump

2 - Animal Chamber

3 - Oxygen Supply

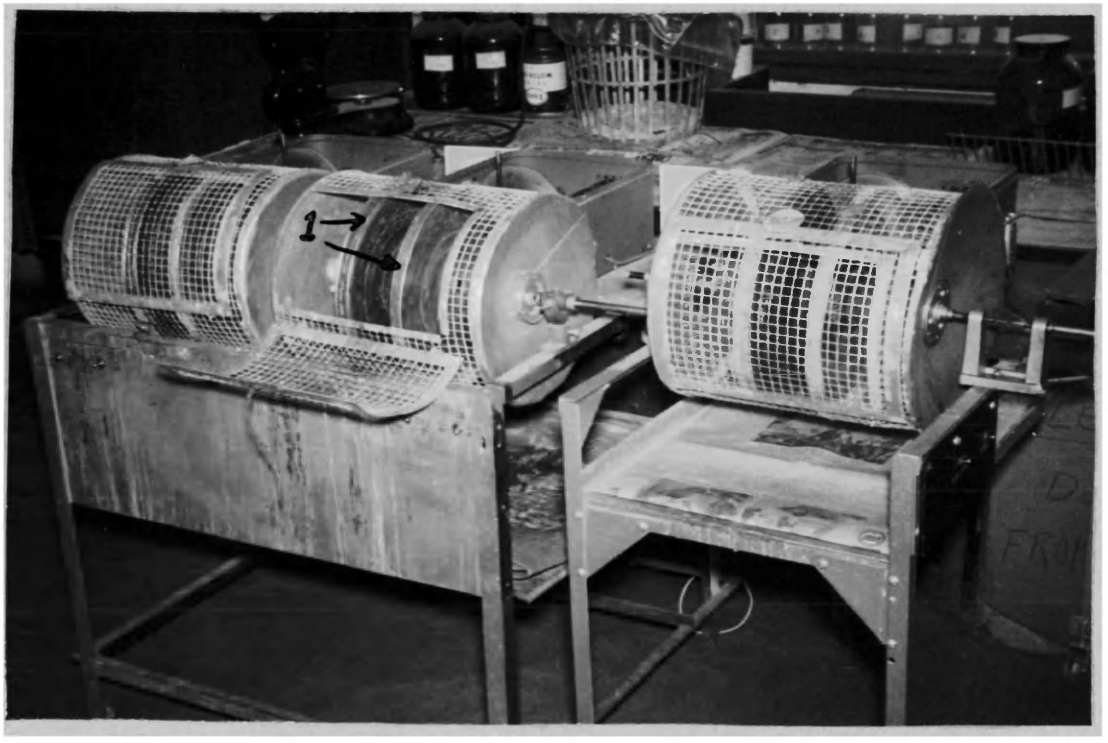
4 - Soda Lime

5 - Kymograph

6 - Concentrated Hydrochloric Acid

PLATE 2

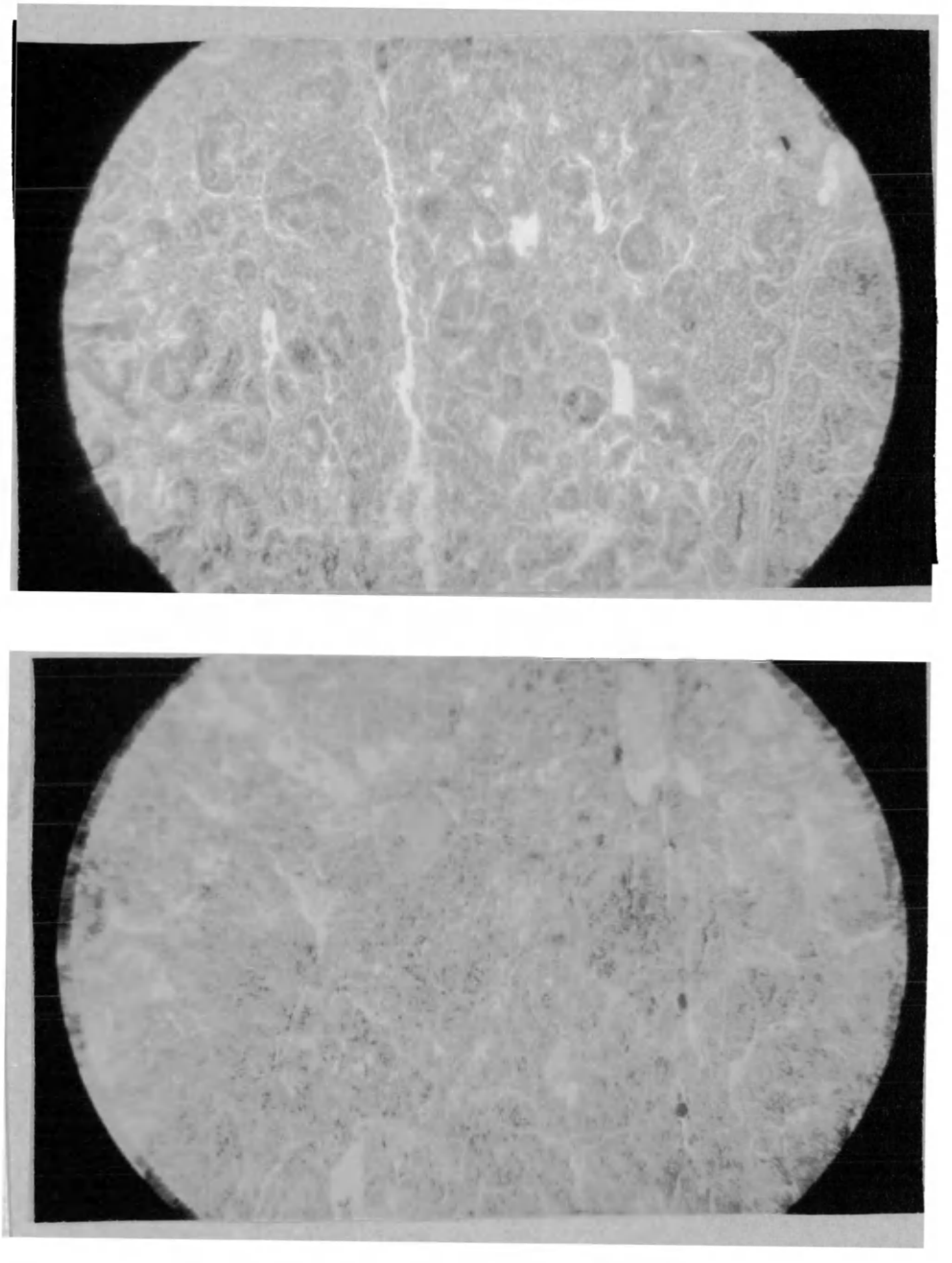
Revolving Cages Used to Stress Birds on Normal Diet and on Diets Containing Thiouracil and Protamone, and Birds Injected With Androgen, Estrogen, and Gonadotropin.



1 - Birds were placed between these plates.

PLATE 5

Photomicrographs of Sections of Adrenal Glands of Stressed and Unstressed Chicks Receiving Normal Ration and No Injections.



Upper - Normal Adrenal(100X).

Lower - Adrenal after stress(100X).

VITA SHEET

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The University of Maryland	1949-51	M.S.	June, 1951
The University of Maryland	1951-53	PhD.	June, 1953

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