AN INVESTIGATION OF THE MORPHOLOGICAL CHANGES, HORMONAL INFLUENCES, AND GENETIC FACTORS CONCERNED IN THE RESPONSE OF YOUNG CHICKENS TO CONDITIONS OF STRESS

By

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INTRODUCTION

There are factors associated with the external environment which constitute conditions of stress. The term, stress, has been used so loosely that it is generally conceded that the condition is present with any situation affecting the normal physiological behavior of an animal. Such factors as muscular fatigue, cold, anoxia, emotional strain, toxic injections, and others far too numerous to mention cause a multiplicity of somatic changes in the body. The degree of response elicited by an organism to stress or the kind of condition causing stress varies from species to species and to a limited extent among individuals within a species.

In the words of Selye (1950), "Anything that causes stress endangers life, unless it is met by adequate adaptive responses; conversely anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life and every vital organ and function participates in them." Therefore, it is apparent that an understanding of the physiological adjustments occurring within the organism which enables it to sustain a normal or near-normal livelihood under stress would greatly enhance man's efforts in his ceaseless attempt to better his own plight as well as that of his domestic animals.

There is an insurmountable quantity of literature reporting experiments designed expressly to study the various physiological aspects of an animal's response to stress. However, it has been observed that in only a very limited number of these studies has the

chicken been used as the experimental animal. This observation is both surprising and unfortunate because the chicken has certain outstanding advantages over other animals for such studies. Not only are chickens easily and economically obtained, but their availability in such large numbers from a given sire or dam offer an excellent opportunity for the study of genetic variation in stress responses. The large size and physical independence acquired by the chicken at an early age would also facilitate stress studies in the growing animal.

As will be fully reviewed later, adaptation to stress is essentially an endocrine adjustment with the pituitary and adrenal apparently playing the most important roles. It may be possible that the early response of the growing bird to conditions of stress might reflect its potential ability as an adult to resist disease and adverse environmental conditions or even its reproductive capacity. In this manner a chicken's early adaptation to a mild form of stress could have practical significance, particularly so, if genetically adaptable strains could be developed. Of course, the validity of the foregoing postulation as it relates to reproduction would depend upon a correlation between the efficiency of the endocrine system in stress and its efficiency in reproduction. Some successful poultrymen, in developing superior broiler strains, raised their breeders in adverse environmental conditions. Such a practice may have as its basis of success, the development of genetically adaptable strains through "natural" selection.

REVIEW OF LITERATURE

The series of somatic changes occurring within the organism as a result of stress stimuli are thought to proceed in a definite chronological sequence. These changes have become known in recent years as the "adaptation syndrome" of Selye. The basic concepts of this syndrome are as follows (Selye, 1950):

1. Phase of Shock. This phase of the "adaptation syndrome" is recognized by such changes as (one or more of the following may not occur):

   (a) a reduction in body temperature
   (b) a state of hypotension
   (c) a generalized tissue breakdown
   (d) a deficiency of chlorides in the blood
   (e) a high level of potassium in the blood
   (f) a state of acidiosis
   (g) an initial rise, then a reduction in blood sugar
   (h) a reduction, then increase in blood lymphocytes
   (i) gastrointestinal erosions
   (j) an emission of certain adrenal hormones may occur in this phase as a result of corticotrophin, but this event is actually a part of the next phase.

2. Phase of Counter Shock. During this phase, there occur a number of changes which assist the animal in its defense against the stress stimuli. The adrenal cortex undergoes a marked hypertrophy which is apparently accompanied by an increase in the activity of this gland. There is also an outstanding involution of the thymus and other lymphatic glands. In addition, most of the changes listed under the phase of shock are reversed in this phase.

3. Stage of Resistance. This phase of the syndrome is recognized as the extended period of time during which the animal successfully resists the stress stimuli. It is the stage

of resistance.

4. Stage of Exhaustion. During this stage, the defense mechanism of the animal fails because of the continued exposure to stress. Many of the changes noted in the phase of shock return. Unless the stress stimuli is removed, the animal dies.

The volume of literature which supplied the evidence for these proposed stages is tremendous. Therefore, the review of literature to follow must, of necessity, consider only those studies which bear directly on the problems of the present experiment. Furthermore, the importance of various physiological changes occurring in the stress response will be considered without too much attention to detail.

THE ADRENAL GLANDS - One of the earliest discernible morphological changes occurring during the organism's resistance to stress is adrenal hypertrophy. Andersen (1935) observed that rats subjected to muscular exercise for a total of four hours during a period of eight hours displayed enlarged adrenals, with a marked widening of the cortex. A similar enlargement was shown by Ingle (1938) for the adrenals of anesthetized rats, the gastronemius muscle of which was made to lift 100 grams three times per second for twelve hours. A number of investigators have also noted enlargement of the adrenals of rats exposed to low barometric pressure (Thorn, et al, 1942; Dohan, 1942; Langley and Clark, 1942; Tornetta, et al, 1943; Dalton, et al, 1944; and Edelman, 1945) and cold (Dugal and Therien, 1949 and Sealander, 1950).

The importance of the adrenal glands in the stress response has been exemplified by an almost complete loss of resistance to stress stimuli following adrenalectomy. Ungar (1947) reported that this lost resistance can be restored by whole adrenal cortical extracts (ACE). Ingle and Nezamis (1949) found that adrenalectomized rats subjected to faradic stimulation of the hind legs had a work output which was proportional to the amount of ACE administered. Adrenal cortical extracts have also been shown to increase the survival rates of normal rats exposed to low barometric pressures (Thorn, et al, 1945) and also of normal mice (Kottke, et al, 1948). Ingle (1944) demonstrated that large injections of ACE enhanced the resistance of normal rats to peptone shock.

The hypertrophy and hyperactivity of the adrenals in animals subjected to adverse conditions is apparently controlled by the pituitary, which releases adrenocorticotrophic hormone ACTH into the blood stream. But the mechanism responsible for the stimulation of the adrenals is very likely more complex than through the simple release of a single pituitary hormone. Paschkis, et al (1950) reported that the levels of adrenal cortical hormones increased following an injection of ACTH and also following an injection of adrenalin. The results of Vogt (1944) gave evidence to indicate that adrenalin has in indirect control over the activity of the adrenal cortex through the sympathetic nervous system. It was shown that this control was not mediated through action by adrenalin on the pituitary. A clarification of the fundamental processes involved in the pituitary-adrenal relationship has been handicapped because of inadequate means for isolating a given pituitary

hormone in a pure form. Noble and Collip (1941) found the corticotrophic effect of some pituitary extracts could be augmented by the simultaneous administration of other extracts, especially of a dilute saline suspension of the whole gland. However, there is ample evidence to indicate that the release of ACTH is controlled by the concentration of the cortical hormones in the body fluids. Sayers and Sayers (1947) concluded that the pituitary releases ACTH at a rate which is inversely proportional to the level of cortical hormone (S) in the body and according to the requirements of the peripheral cells for cortical steroids. An excessive dose of a single adrenal hormone is apparently sufficient to interfere with this process. It was shown by Selye and Dosne (1942) that an overdosage with desoxycorticosterone acetate inhibited the response of the adrenal cortex of rats to various stimuli. As a result of this inhibition, the animals indicated a lowered resistance to adverse conditions and toxic injections. It was concluded by these investigators that an overdosage with one hormone produced by an endocrine cell can interfere with the production by the same cell of the other hormonal compounds.

There seems to be both an abundant and rapid release of the adrenal cortical hormones by the adrenals of animals exposed to stress. Vogt (1947) found that phenomenally large amounts of cortical hormones were released into the blood from the left adrenal of a dog. This investigator observed that the left gland of an animal under mild operative shock was producing 19 times as much hormone per minute as could be obtained from the extracted gland. Furthermore, it was shown that the venous blood from the adrenal of the cat, dog, goat, pig, or rabbit

would prolong the survival time of adrenalectomized animals exposed to cold. The heart blood, on the other hand, had no effect. The rapidity with which the adrenal hormones are apparently released by the adrenals of animals exposed to stress is also amazing. Nichols and Miller (1948) reported that there was a significant excretion of the adrenal corticoids in the sweat of two subjects exposed to strenuous exercise in heat for 30 to 45 minutes. Since this rate exceeded the resting values for renal excretion, it was proposed that this might indicate an activation of the adrenal cortex. Paschkis, et al (1949) demonstrated that a rise in the cortical hormone in the arterial plasma of the dog occurred within the first hour after subcutaneous injection of formulin. Gray and Munson (1950) found evidence to indicate that ACTH was released in a matter of seconds following histamine injection into the rat. It was proposed by Tepperman, et al (1947) that cholesterol may be a precursor of the adrenal hormones. These workers reported that the cholesterol ester content in the adrenals of rats exposed to low barometric pressures was reduced. In this respect, Levin (1945, a, b) found that rats subjected to 0° to 5° C. for 16 to 22 hours revealed small decreases in adrenal cholesterol. Histologic evidence was presented by Darrow and Sarason (1944) which demonstrated that there was a depletion in adrenal cortical lipid in the adrenal of rats exposed for only two hours at low barometric pressures.

By administering gradually increasing doses of a given stress stimuli to rats, Selye (1938 b) found that it was possible to develop demonstrable resistance in the animal to the stress stimuli. Furthermore, it was shown by this investigator that the resistance to one type of stimuli was apparently specific, and a decrease in the resistance to

other stimuli usually resulted. Rats pretreated with progressively increasing doses of one toxic substance were able to withstand doses which were normally lethal. But a sub-lethal dose of another agent was frequently lethal. One interesting aspect of the resistance is the observation that it is not completely lost following adrenalectomy. Selye, (1937) demonstrated that resistance acquired to drugs, muscular exercise, and cold was retained after adrenalectomy. It was proposed that the trained tissues apparently require very little if any cortin for the performance of their functions. A discrepancy to this observation was reported by Desmarais, (1949) who found that the resistance acquired to cold by rats was lost when the adrenals were removed. But Langley, (1943) observed that rats which were adrenalectomized after 6 days continuous exposure to 20,000 feet altitude were more resistant to continued exposure than adrenalectomized animals which had not been pretreated. In this instance, it was found that 0.5 cc of ACE was sufficient to prevent death in the pretreated animals, but did not prevent death in the untreated animals.

THE LYMPHATIC ORGANS - During the alarm reaction, there is a marked and progressive atrophy of the lymphatic organs. Foglia and Selye, (1938) observed that the alarm reaction elicited by means of muscular exercise, subcutaneous injections of formaldehyde, surgical shock, or exposure to cold was accompanied by a pronounced regression in the thymus, spleen, and lymph glands. This response was shown not to be species specific because it was seen to occur in the rat, guinea pig, rabbit, and cat. It has been established that this involution is the result of a release of cortical hormones. Selye, (1936 a, b)

concluded from experiments with rats that the adrenal secretes a substance which is responsible for the thymic atrophy. It was found that various operative injuries and drugs which normally caused thymus regression were without effect if the animals had been adrenalectomized. They were found to have some effect in hypophysectomized animals, but to a much less extent than in normal animals. The results of Simpson, et al, (1943) demonstrated that ACTH failed to cause thymic involution in the rat if the animals had been adrenalectomized. Stoerk, (1944) found that adrenalectomized animals exposed to adverse conditions revealed less atrophy of the thymus than the normal controls. It has also been shown that the recovery rate of an involuted thymus is much more rapid in the absence of the adrenal. This work was performed by Gregoire, (1943), who used X-rays to cause involution. Cortisone was found by Antopol, (1950) to cause an atrophy of the thymus and spleen in mice. Molomut, et al, (1950), also using mice, observed that 4 mg. of cortisone in a two-day period caused a 21 per cent reduction in spleen size. Since continued treatment with cortisone did not increase the original depletion, it was assumed that the effect is rapid and maximal.

It has been proposed that the thymus may have some influence upon the function of the adrenal. In a study with rats reported by Selye, (1940) it was found that saline extracts prepared from the lymphatic tissue (lymph glands, spleen and thymus) of adrenalectomized animals are more toxic for adrenalectomized rats than similar extracts prepared from the lymphatic tissue of normal animals. This toxicity was more acute if the adrenalectomized animals from which the lymph extracts were taken had been subjected to exhaustive muscular exercise

just prior to sacrifice. This investigator proposed that toxic metabolites may be formed under the influence of the exhaustive exercise and that the adrenals are necessary if these metabolites are to be detoxified. A study was conducted by Segaloff and Nelson, (1940) to ascertain whether thymectomy would alter the course of adrenal insufficiency in the bilaterally adrenalectomized rat. It was found that thymectomy failed completely to produce any effect.

Substances other than ACE are known to affect the morphology of the lymphatic glands. The role of the sex hormones in thymic regression is the classic example. Persson, (1949) has shown that the spleens of gonadectomized guinea pigs contain considerably more lymphatic tissue. This investigator also observed that the spleen of oestradio-treated animals were much enlarged but contained a relatively small amount of lymphatic tissue. Stoerk, (1944) observed that castrated rats exposed to sub-optimal conditions showed less thymic atrophy than normal controls. Injections of insulin were found by Zeckwer, (1948) to cause shrinkage of lymphatic tissue in rats. Riddle, (1941) reported that daily injections of pigeons with insulin resulted in adrenal hypertrophy with the effects more pronounced in the cortical cells than in the medullary cells. It was proposed by the former investigator that the shrinkage of the lymphatic tissue may be mediated by the release of adrenalin in response to insulin hypoglycemia. As mentioned earlier, Vogt, (1944) found that adrenalin causes a stimulation of the adrenal cortex, resulting in a release of the cortical hormones. Synonymous with thymic atrophy is growth inhibition and weight loss. Selye, (1951) found that growth hormone elim-

inated the inhibition of growth and the weight loss caused by multiple sterile turpentine absesses. And Feldman, (1951) found that the administration of growth hormone to hypophysectomized rats results in an increase in the weights of the spleen and thymus. The administration of thyroxine has also been shown to increase the weights of the spleen and peripheral lymph nodes of male mice (Marder, 1949).

The process whereby cortical hormones cause involution of the lymphatic tissue has attracted the interest of many investigators. There is ample evidence to indicate that the involution is caused, at least in part, by the effects which these hormones have on the different leucocytes. In the discussion to follow it will be shown that the cortical hormones apparently mediate the breakdown of lymphocytes and basophils. At the same time, however, there occurs a neutrophilia which is quite pronounced, so much so in fact that an absolute leucocytosis is observed despite the reduction in the lymphocytes and eosinophils.

Meyer, et al, (1935) observed that rats exposed to low barometric pressures developed an early leucocytosis which is followed by leucopenia. A brief period of exercise was found by Gerkin and Miller, (1949) to cause a 60 to 100 per cent increase in the leucocyte count. Mice placed at 5° C. were found by Elmadjian and Pincus, (1945) to show a decrease in the number of circulating lymphocytes. This reduction was not noted if the animals were adrenalectomized prior to exposure. It was reported by Munro and Noble, (1947) that the reduction in the circulating lymphocytes in traumatized rats was proportional to the amount of trauma. The daily count of circulating

eosinophils in men were significantly reduced by exercise according to the results of Bader, et al (1948). Seven of 9 drivers considered at the Indianapolis Speedway (1950) showed at least a 90 per cent drop in circulating eosinophils after the race and the remaining 2 men showed at least a 60 per cent reduction. It was concluded by Harlow and Selye, (1937) that during the alarm reaction, there is an increase in the total white blood cell count mainly as a result of neutrophilic leucocytosis. Along with this occurrence, however, there is a relative lymphopenia. If the alarming stimuli were very severe, a period of leucopenia precedes this characteristic reaction.

More direct evidence for the effects of cortical hormones on the leucocytes has been gained through the use of ACTH and ACE. Reinhardt and Li, (1945) reported that either subcutaneously or intraperitoneally administered ACTH caused a rapid reduction in the number of lymphocytes in the thoracic duct lymph. A condition which did not occur if adrenalectomized animals were used. On the other hand, Reinhardt, et al (1944) found that intraperitoneal injections of ACTH in dogs produced a marked neutrophilic leucocytosis. ACTH and cortisone were found by Dworetzky, et al (1950) to reduce the number of eosinophils in the blood of male and female guinea pigs. This effect was not observed in pregnant females injected with ACTH. Hechter and Johnson, (1949) observed that ACE in the presence of lymphoid tissue homogenates significantly increases the rate of lymphocyte breakdown. It was shown by Hechter, (1948) that ACE administered to the isolated rabbit spleen, perfused with whole blood under constant pressure, caused an immediate discharge of

splenic lymphocytes into the circulation. Secondarily, there was a tendency for the number of circulating lymphocytes in the perfusion medium to decrease. A single injection of ACE into the White Leghorn produced leucopenia and a pronounced lymphopenia. In view of the foregoing discussion, it is interesting that the condition of leucopenia was observed. Subcutaneous injections of cortisone into mice was shown by Guittner, et al (1951) to cause a prolonged fall in circulating lymphocytes and eosinophils.

Speirs and Meyer, (1949) reported that injections of adrenalin produced a large reduction in the circulating eosinophils of mice. Removal of the adrenal cortex prevented this condition. Adrenalin was shown by Gellhorn and Frank, (1948) to cause a neutrophilic leucocytosis and a marked lymphopenia. The absolute lymphocytosis produced in swim-stressed normal rats by injection of ACE was prevented by Stone and Hechter, (1948) through removal of the spleen and adrenals. It was proposed by the investigators that ACE may induce splenic lymphocyte discharge into the circulation. A satisfactory explanation cannot be offered for the production of a condition of lymphocytosis instead of lymphopenia by the adrenalin injection. Dury and Bacchus, (1949) also concluded that the spleen and adrenal are necessary if a significant depression in the circulating eosinophils were to follow adrenalin treatment.

THE ADRENAL GLANDS AND THE DEFENSE MECHANISM - There is evidence which indicates that lymphocytes synthesize and later release into the blood stream the normal gamma globulin of the plasma and also the numerous antibodies appearing in the blood during immunity reactions.

Antibodies, of course, are known to be specific modifications of gamma globulins. Dougherty, et al (1944) reported that per unit of extractable nitrogen, lymphoid tissue had significantly higher agglutin and hemolysin titers than did the sera of the same animals. The animals used were mice which had been previously immunized to sheep erythrocytes. Observations made by Harris, et al (1945) caused these investigators to conclude that antibodies were produced within the lymphocyte and not absorbed from the surrounding fluids.

Apparently the adrenal cortex is involved in the lymphocyte. White, (1950) in a review which considered the relationship of the adrenal cortex to the immunizing mechanism concluded that the adrenal probably plays the following role:

1. The level of secretory activity of the adrenal cortex is influenced by the administration of an antigen, since antigens may elicit, in a non-specific manner, pituitary-adrenocortical secretion.

2. An increased level of circulating adrenocortical steroids has a profound effect on cells of the reticulo-endothelial system, namely macrophages and lymphocytes, which are possibly concerned with the processes of antibody formation and release.

3. The rate of formation of antibodies by specific tissue is considerably influenced by adrenocortical secretion.

These conclusions are not lacking in experimental proof. A number of investigators have shown that the protein and antibody content of the blood is altered during the stress response. Chanutin, (1947) revealed that the serum of dogs injured by mustard, heat, cold, or turpentine injection contained higher levels of alpha and beta globulins. The research of Dougherty, et al (1945) showed that adrenal cortical mediation is necessary for the release of antibodies from the lymphocytes. These workers observed that benzene

and potassium arsenite liberated antibodies from the lymphocites of intact mice. However, these stimuli failed to effect this release if the mice had been adrenalectomized. Single injections of adrenotrophic hormone or the adrenal steroids into rabbits were found by White and Dougherty, (1945) to significantly increase the beta and gamma fraction of the blood. These investigators (1946) observed that any stimulus or stress which augmented pituitary-adrenal cortical secretion accentuated lymphocyte dissolution and globulin release. It was suggested by these workers that one of the major functions of the lymphocytes may be to serve as a medium for distributing gamma globulin throughout the body; and also that the rate of release of this protein is controlled by the pituitary by way of the adrenal cortex. The results of Trowell, (1947) revealed that hormones of the adrenal cortex stimulated the dissolution of lymphocytes in the germinal centers.

On the basis of the foregoing observations, it would be expected that the administration of adrenal cortical hormones to an organism should augment the rate at which antibodies are released following an invasion of the antigen. There are results which implicate that this relationship may actually exist. The adrenal cortex of female rabbits infected with bacterial pyrogens was noted by Windle, et al (1950) to show signs of involution after an earlier phase of marked growth stimulation. Dougherty, et al (1944) reported that in rabbits the agglutin titers to sheep erythrocytes were enhanced as a result of adrenal cortical injections. With continued hormone injections, these elevated titers were maintained

for two weeks. Chase, et al (1946) observed that the rate of antibody production to sheep erythrocytes was increased in mice, rats, and rabbits by the subcutaneous injection of aqueous adrenal cortical extract at the time of antigen administration. Adrenal cortical extracts also increased antibody production in mice and rabbits receiving as antigen either staphylococcal toxin, horse serum, or egg albumin. These investigators found that the final antibody titer reached when hormone was given together with antigen was approximately twice as great as in animals receiving antigen alone. It was shown by Bissett, (1949) that the release of serum agglutinins which was inhibited at low temperatures in frogs and fish is restored by injection of adrenal cortical extracts. But Houghton, et al (1947) and Thatcher, et al (1948) did not observe increase agglutin titers when intact and adrenalectomized cats were given the antigen with adrenal cortical extracts. Similarly Roberts and White, (1951) found that in general, the rate of development of hemolysin titers in the tissue and serum of rats injected with a single intravenous dose of sheep erythrocytes could not be altered significantly by changes in the circulating adrenal cortical hormones. However, the rate of release of antibody to a serum medium in vitro by splenic tissue was significantly affected by the degree of adrenal cortical activity. No new formation of antibody occurred in incubates of splenic tissue obtained from adrenalectomized animals. These investigators believed the discrepancy between the in vivo and the in vitro results might be explained by the observation that antibody uptake by various tissues in vitro, particularly by liver and

mesenteric lymph nodes (Roberts and White, 1950), may be depressed by previous adrenalectomy and possibly enhanced by injection of adrenal cortical hormones. An experiment was conducted by Scott, et al (1933) in which guinea pigs received diphtheria toxin; rats received Trypanosoma equiperdumin; and mice received pneumococcus. No benefit was shown in these experiments following the administration of adrenal cortical hormones. It was proposed that the doses used might have been insufficient.

Other observations made by a number of investigators give further evidence for a relationship between the adrenal and the defense mechanism. The relationship indicated in many instances, however, does not suggest an involvement of antibody release. In 1918, Winter, (1918) observed that the adrenals of three influenza patients were disintegrated and haemorrhagic. Drake, et al (1944) made an histophysiologic study of the adrenal medulla in 125 patients dying as a result of various diseases. In neoplastic diseases and in long-standing infections, the evidence indicated that the activity of the medulla had been decreased. High activity was noted in injuries of the brain, in diabetes, in obesity, and in thyrotoxicosis. Twenty-six cases of hypertension not associated with the kidneys (inflammation) were included in the series. In all except two, histologic evidence of hyperfunction of the medulla was present. Ball and Samuels (1938) observed that the adrenal weights of tumor-bearing rats were greater than controls. These investigators proposed that either toxins from the tumors or a changed general metabolism might have been responsible for this enlargement.

Further evidence for the relationship between the adrenals and the defense mechanism has resulted from a number of studies in which attempts have been made to alleviate the symptoms of a disease with adrenal cortical hormones. It was reported by Webster, (1950) that patients with a number of liver diseases (four patients with cirrhosis, one with homologous serum jaundice, two with arsenical hepatitis, and one with chronic hepatitis with "pseudo-colic") recovered promptly and laboratory tests rapidly reverted to normal after treatment with adrenal cortical extracts.

Since their isolation, the adrenal cortical hormones, cortisone and desoxycorticosterone, and the pituitary hormone, ACTH, have been employed in the treatment of a number of maladies. The work relating to the use of the first in the treatment of rheumatoid arthritis has been widely publicized. But the relief obtained after treatment of this disease with cortisone is apparently only temporary as shown by the work of Anderson, et al (1951) with humans and the work of Doyle, et al (1950) with swine. Anderson and Bolin, (1946) found that desoxycorticosterone acetate failed to modify the mortality of Swiss mice to adapted poliomyelitis virus. While not directly associated with the adrenals, it was interesting that these workers found that progesterone gave complete protection, while treatment with stilbestrol decreased mortality from 68 per cent to 2.5 per cent, compared with a decrease to 20 per cent when testosterone propionate treatment was used. It was shown by Kilbourne and Horsfall, (1951) that adult mice ordinarily resistant to Cosackie virus, may be lethally infected if preliminarily administered cortisone. The

failure of resistance to be enhanced or even maintained following treatment with cortisone might possibly be reflected in the effect which this hormone has on the production of adrenocorticotrophic hormone (ACTH) by the pituitary. Evidence was presented by Selye and Dosne, (1942) which indicated that a high level of cortisone might reduce the quantity of ACTH, thereby interfering with the production of other adrenal hormones.

The effect of ACTH and cortisone on phagocytosis was studied by Crepea, et al (1951). These investigators found that in 9 of 10 patients under treatment with ACTH or cortisone, the phagocytic activity of the neutrophilic leucocyte decreased. In the remaining case an increase was observed which was shown to be due to the development of a specific antibody during treatment. Sternberg, et al (1952) reported that cortisone, administered orally or intramuscularly, produced complete healing of atopic dermatitis in 23 of 24 patients. One patient was intolerant to cortisone, but responded to subsequent cortitrophin (ACTH) treatment. It was concluded by Franklin, et al (1952) that both ACTH and cortisone are effective and practical agents for the treatment of asthma. Moyer, et al (1950) reported that adequate doses of ACTH shows an inhibiting action upon the occurrence of clinical manifestations and the development of pathological lesions in experimental allergic encephalomyelitis of the guinea pig. Results obtained by Campbell, et al (1951) suggested migraine may result from over secretion of adrenal cortical hormones. It was found that after drinking 1500 ml of water, 16 migrainous subjects showed a diuresis similar to that of seven

normal subjects but excreted much more Na and Cl. The concentration of Na in the blood was found to be high before and especially during an attack of migraine.

ADDITIONAL BLOOD CHANGES - It will be recalled that a hormone, by definition, depends upon the blood stream as the means for reaching its target organ(s). Yet probably no hormone is carried by the blood which does not affect either directly or indirectly the blood and its constituents in one or several ways. The pronounced effect of ACE on the lymphocytes of the blood has already been considered. But a number of additional changes have been observed in the blood of animals exposed to various stress stimuli. Many of these have been thought to be mediated directly through hormones, and some as being the result of other physiological factors.

The adrenal hormones apparently affect the resistance of red cells to hypotonic lysis because it has been shown that removal of the adrenals increases this resistance (Megel and Gordon, 1951). Administration of ACTH for 116 days to intact rats was found by Garcia, et al (1951) to cause an increase in the total circulating red cell volume. This hormone was also shown by these investigators to prevent the decrease in the total circulating red cell volume which is normally found in the hypophysectomized rat. Feigin and Gordon, (1950) reported that exposure of hypophysectomized rats to altitudes of 16,000 feet for 6 hours of each day for 14 days caused no significant effects upon the peripheral red cell values, hemoglobin levels, or bone marrow histology. Intact rats responded to this altitude

with increased numbers of red blood cells and increased hemoglobin values. However, a simulated altitude of 22,000 feet for similar periods was found to cause an erythropoietic response in the hypophysectomized rats of approximately the same magnitude as that displayed by unoperated controls. These investigators concluded that the pituitary seems to be essential for the erythropoietic response at 16,000 feet but that the full effect can be produced in the absence of this gland at 22,000 feet. Cole, et al (1944) noted a number of blood changes in rabbits which had been suspended head up without anesthesia for 24 hours. The animals thus treated became unconscious within 20 to 120 minutes and 30 per cent of the animals died within 24 hours. Rabbits treated in this manner showed: (1) a drop in blood pressure, (2) metabolic acidiosis, (3) decreased blood carbon dioxide and venous oxygen, (4) increased plasma lactate, phosphate, pyruvate, potassium, and non-protein nitrogen, (5) an increase or decrease in plasma glucose, and (6) a decrease in plasma chloride.

Cortisone was shown by Adlersberg, et al (1950) to cause an average increase of 15 per cent in the total serum cholesterol of 15 patients. The phospholipids increased an average of 26 per cent with 14 of the 15 showing this change. In the 12 instances where the neutral fat was calculated, there was an average decrease of 51 per cent. Less pronounced changes were produced in the serum lipids by the administration of ACTH. A small drop in total serum cholesterol was noted in 6 of 9 patients during the first few days of treatment. An average increase of 9 per cent in the phospholipids

was observed with 9 of the 12 observed exhibiting a rise. There was an average decrease of 16 per cent in the neutral fat, with 6 of 8 showing this effect. None of the changes occurring with ACTH therapy were statistically significant. Selye, (1939) found that excessive muscular exercise caused a considerable increase in the lipid content of the liver. This increase was more pronounced (1) in adults than in young animals, (2) in fasted animals than in non-fasted animals, and (3) in females than in males. MacLachlan (1939) found that the plasma lipids of rabbits decreased after 3 hours exposure to low pressures (254 mm. Hg.). By the end of 6 hours exposure, the initial levels had been reestablished. No effect was noted on the lipids of cats and dogs exposed to similar conditions. It was concluded by the investigator that the difference in the response of rabbits from that of cats and dogs may be related to their ability to utilize fats.

Cats were found by Smith and Oster, (1946) to show a marked increase in blood sugar after exposure to low oxygen tension. It was shown by Stickney, et al (1948) that 15 minutes at 24,000 feet was sufficient to cause hyperglycemia in the average dog. Exposure to 28,000 and 32,000 feet for the same period of time invoked proportionately greater elevations in blood sugar. When the length of exposure at 28,000 feet was varied from 15 to 60 minutes, the maximum rise was seen at the end of 30 minutes. Blood sugar then declined with continued exposure. Selye, (1939 a) found that the blood sugar of rats decreased under the influence of muscular exercise, but a marked secondary rise was indicated during the recovery period even if the animals were fasted. This investigator (1938 a) reported that

adaptation to histamine, cold, or formaldehyde treatment entailed an initial transitory hyperglycemia followed by hypoglycemia. later, when adaptation is acquired, the blood sugar rises above the initial value again and finally in the stage of exhaustion, a second sharp fall of the blood sugar occurs which frequently caused hypoglycemic convulsions and death.

Rakestraw, (1921) conducted a rather detailed study in which he considered the effect of muscular exercise on certain of the blood constituents of 21 subjects. In this study, two types of exercise were employed. The first of these was short strenuous effort which was represented by a 100 yard dash or by running one mile. The second was longer and more tedious, being represented by a 65 mile bicycle ride over a period of 12 hours. Short strenuous exercise was found to increase blood sugar concentration, both in plasma and corpuscles, while a longer period of exercise was generally accompanied by a drop in blood sugar which was greater in the plasma than whole blood. It was noted that both kinds of exercise were accompanied by small increases in uric acid by about the same order, which was greater in the plasma than in the whole blood. No effect on urea or non-protein nitrogen was caused by short, strenuous work, but longer work caused a slight increase in both, in whole blood as well as in the plasma. The viscosity of whole blood was found to increase considerably and that of the plasma slightly. Though there was no discernible change in blood volume, the specific gravity, hemoglobin, and the number and relative volume of corpuscles were found to increase during the periods of exercise. It was noted by Selye, (1939) that the red cell concen-

tration of rats decreased in the recovery period following intense muscular exercise.

The blood chloride was found by Selye, (1939 a) to show an initial decrease in animals treated with histamine, cold, or formaldehyde. But during the stage of resistance, an increase in this component was noted. In 1939 a, this investigator reported that intense muscular exercise caused a marked hyperchloremia in rats which is maintained for several days following discontinuation of exercise.

Certain morphological changes in the circulatory system of animals exposed to stress have also been observed. Highman and Altland, (1949) exposed rats 14 days of age at 25,000 feet for 4 hours each day until death occurred. None of these animals lived for more than one-half the expected life span. Their hearts were enlarged and contained thickened valves. Nearly all the rats had striking vascular engorgement and severe lesions in various organs. In some animals, death was caused by an accumulation of blood in the intestine. Kondo and Katz, (1945) found that the heart size of dogs was decreased when shock was induced by venous occlusion of the hind limbs. This decrease was greatest during the first hour with a continuous decline until a short period prior to death, when a leveling off occurred. The survival time of these animals ranged from 30 minutes to 6 hours. This decline in heart size was attributed to the loss of circulating blood as shock developed, the rate of loss lessening as the experiment progressed.

NUTRITION - Nutrients and their metabolism in the body have been shown to be greatly influenced by conditions of stress. There is

evidence to indicate that any situation causing stress may increase the animal's requirements for one or more nutrients. Frequently, an increase in metabolism may be responsible for this observation. A chronic deficiency of a required nutrient has been found sufficient to invoke the typical stress response.

Among the organs which aid the body in resisting the effects of cold, one of the most common stresses to which man and animals are exposed, the adrenals are of prime importance. The work of Horvath, et al (1938) revealed that there was a 22 per cent increase in heat production when non-adrenalectomized rats were placed at 4° C. after being held at 29° C. The corresponding increase in the heat production of unilaterally adrenalectomized animals was only about 7 per cent. The maximal heat production of these animals was attained more slowly than in the control animals. Horvath, (1938) reported that double adrenalectomy caused a 10.6 per cent decrease in heat production measured at 29° C. after 1 to 2 hours at 4° C. This observation compared with an increase of about 20 per cent in the control animals.

Adrenals of rats maintained in cold were observed by Reiss and Halkerston, (1950) to show an increase in ^{32}P uptake. These workers concluded that this reaction was due to endogenous mobilization of ACTH since hypophysectomized animals failed to show it. The phosphorylation in the adrenals of hypophysectomized animals was considerably decreased, but a 50 per cent increase resulted within an hour after an intravenous injection of ACTH into these animals. Aub, (1920) found that traumatic shock induced in anesthetized cats caused a 30 per cent drop in metabolism. Shock was produced by crushing both

hind legs of these animals. The quantity of food consumed by white mice was found by Donhoffer and Vonotsky, (1947 a) to increase at low temperatures and decrease at high temperatures. These observations were found to be the result of an increase or decrease in the consumption of carbohydrate rich food. In this study, free selection of foods rich in carbohydrates, fat, and protein was allowed. It was suggested that changes in thyroid function might play a role in the qualitative regulation of food intake. Donhoffer and Vonotzky, (1947 b) found that when mice were given thyroxin and free choice diets, starchy food ingestion was increased. At the height of the effect of thyroxin this often provided 80 per cent of the calories while in the untreated animals 70 to 80 per cent were furnished by the selection of fat rich food. The foregoing observations cause one to view the work of Dugal, et al (1945) with even greater interest. These investigators found that a diet rich in fats was decidedly superior to one rich in carbohydrates (both diets being equicaloric and equivitaminic) for adaptation and resistance to cold. In contrast, a diet rich in carbohydrate and poor in fats was much more favorable than one rich in fats for conferring resistance to heat. Ingle, (1945) found that a diet high in carbohydrates results in a marked hypertrophy of the adrenals while a casein diet high protein did not. However, a high casein and lactabumin diet caused a definite increase in adrenal weights above those of similar animals fed a high carbohydrate diet. It was observed by Moya, et al (1948) that adrenal cortical stimulation of rats elicited by cold or by unilateral adrenalectomy was greater in animals kept on high (30%) rather than

low (15%) protein diets. This difference in dietary protein concentration did not affect the adrenals of normal animals under basic conditions; nor did such diets affect the adrenal response of hypophysectomized rats injected with ACTH. These investigators concluded that these diets do not sensitize the adrenal to ACTH nor do they normally increase ACTH secretion by the pituitary. But when the adrenal growth is stimulated beyond normal, the high protein diets further augmented ACTH response either by increasing ACTH production or by synergizing the hypophyseal principle. Roofe and Brown, (1948) considered the effects of diets containing 0, 2, and 18 per cent protein on the cervical lymph nodes of rats. The last level was fed to the control group and the 3 diets contained all other nutrients known to be essential. There was a depression of the medium sized lymphocytes in the nodular areas of the animals on the 0 and 2 per cent protein diet, while the small lymphocyte was increased markedly. The reverse was found to be true in the internodular area. The 18 per cent protein diet seemed to depress the medium sized lymphocytes in the medullary cords but showed an increase in small cells. In the depleted rats, the medium sized lymphocytes were increased above normal in the sinusoidal areas while the small lymphocyte were depressed. The large lymphocytes and reticular cells remained constant on all diets in all 4 areas. In males, the cell population was greater than in females except for the medium sized lymphocytes in the internodular area and medullary sinuses, and the large lymphocyte in all areas.

It was shown by Blumenthal, (1934) that even the manner in which animals are fed can exert a discernible influence on the mitotic activity of the adrenal cortex and the thyroid. This investigator found that if guinea pigs were fed once in 24 hours, an increase in mitotic activity occurs in these glands which reaches a maximum between the fourth and twelfth hour following feeding. Prolonged starvation has been shown to cause adrenal hypertrophy with an increase in total fat and a disappearance of birefringent lipid granules (Elliott and Tuskett, 1906; Findlay, 1921; and McCarrison, 1922).

The apparent relationship existing between the adrenal gland and ascorbic acid (vitamin C) has attracted the interest of a number of investigators. Deane and Morse, (1948) concluded that virtually all the cells of the rat's adrenal cortex contained ascorbic acid (or a reducing substance of similar activity). But when the glands lost the capacity to synthesize steroid hormones, the reducing substance was also lost. Since the guinea pig, as man, fails to synthesize this vitamin, it is dependent upon an exogenous source. It is, therefore, an excellent animal for studying the effects of a vitamin C deficiency. Such a deficiency in the guinea pig has been shown to cause adrenal hypertrophy (Quick, 1933; Baldwin et al, 1944; and Clayton and Prunty, 1951). Hyman, et al (1950) reported that cortisone and ACTH prolonged the life and reduced the hemorrhagic manifestations of scurvy in guinea pigs. An observation which was not confirmed by Clayton and Prunty, (1951). Lockwood and Hartman, (1933) found that ACE injections improved growth and lessened

the other effects caused by a vitamin C deficiency in guinea pigs. It was reported by Stepto, et al (1950) that guinea pigs receiving no ascorbic acid in their diet displayed a marked reduction in adrenal ascorbic acid, adrenal cholesterol, and liver glycogen. In animals which received 0.5 mg. of ascorbic acid, there was only a decrease in the adrenal ascorbic acid. No abnormalities were observed when animals received over 2.5 mg. per day. Bourne, (1944) conducted a rather interesting study in which he considered the effect of vitamin C deficiency on the tensile strength of wounds inflicted in guinea pigs. The tensile strength of wounds which had healed for one week were estimated in animals which had been receiving graded doses of vitamin C for 2 weeks. This investigator observed that the tensile strength of the wounds was proportional to the daily dose of vitamin C given. Saturation with the vitamin, however, was not found essential for optimal healing. When the blood vitamin C was less than 0.1 mg./100 cc., a wound was likely to have very low tensile strength.

The ascorbic acid concentration of the adrenal has been shown to be the function of adrenal cortical activity. Hypophysectomy of the rat was shown by Tyslowitz, (1943) to cause a reduction in the adrenal ascorbic acid. It should be mentioned that the testis, liver, kidney, and blood serum of these animals were also reduced in ascorbic acid content. In contrast, adrenalectomy has been found to cause an increase in the pituitary ascorbic acid of the rat (Pomereau, 1949). Sayers and Sayers, (1947) reported that exposure of rats to cold and heat, and injection of histamine, epinephrine, and killed typhoid

organisms brought about a reduction in the concentration of adrenal ascorbic acid. Evidence was presented by these investigators to indicate that elaboration of ACTH by the pituitary during exposure of the rat to stress for a period of one hour or less is proportional to the decrease in the concentration of adrenal ascorbic acid which accompanies such an exposure. Bacchus, (1950) described two types of cells in the adrenal cortex with respect to their diffusion with ascorbic acid. It was indicated that one "type" existed in which the ascorbic acid was diffusely distributed in the cytoplasm, and a second "type" with ascorbic acid peripherally in the cytoplasm. During the alarm reaction, there was a preponderance of the latter type of cells; the resistance phase being characterized by the normal distribution of the "cell types", with the cells being larger than normal. The exhaustion phase was characterized by the occurrence of considerably enlarged cells which exhibited a decrease in ascorbic acid content. The investigator proposed that these shifts may have some significance in the secretory activity of the cells of the adrenal cortex. Booker, et al (1950) observed that when animals under stress were given ascorbic acid, they excreted more ascorbic acid in the urine than was given. This observation indicated both a lack of ability to control the administered ascorbic acid and a loss in ability to retain the stored ascorbic acid. When similar groups of animals were given the same amount of ascorbic acid and injected with ACE, the urinary secretion was significantly less, with notable increases in the plasma and cell levels. Injection with ACTH resulted in a rise in the urinary ascorbic acid which reached a peak on the

third day and fell on the fourth. When the ACTH animals were given ascorbic acid, the urinary output of ascorbic acid was higher by the third day than in the groups given ACTH alone. Following this period, a similar but not so pronounced drop was noted on the fourth day as seen in the animals given only ACTH. Cold exposure was shown by Shepherd, et al (1952) to cause a decrease in the adrenal ascorbic acid in both normal and diabetic rats. Dugal and Therien, (1947) concluded that the rat requires large quantities of vitamin C if it is to become acclimatized to low temperature. Those animals which were unable to adapt themselves to cold show decreased ascorbic acid in tissues; while the animals being able to resist the condition showed an increase in ascorbic acid. Also in this study, the resistance of guinea pigs to cold was found to be proportional to the daily dose of ascorbic acid. Later, these investigators (1949) reported that the typical enlargement of the adrenals which resulted when rats and guinea pigs are exposed to cold could be completely prevented by large doses of ascorbic acid. These animals were also more resistant to cold in spite of the smaller adrenal size. It was concluded that ascorbic acid seems to play a compensatory role somewhat similar to one of adrenal cortical hormones. In addition, normal hypertrophy is prevented, there is no atrophy, but at the same time, the resistance to cold is increased. Therien and Dugal, (1949) found that guinea pigs required more vitamin C as the surrounding temperature is being lowered.

A deficiency of several B-Complex vitamins has been shown to influence the adrenal cortex. Marrian, (1928) reported an enlargement

of the adrenals in pigeons receiving a vitamin B deficient diet. This worker estimated that about 19 per cent of the observed hypertrophy was the result of an edematous condition. Significant enlargement of the adrenals of pyridoxine depleted rats, predominantly involving the zona fasciculata, was noted by Stebbins, (1951). A severe deficiency of this vitamin was accomplished by using the vitamin antagonist, desoxypyridoxine. It was also noted that the quantity of ascorbic acid-like materials in the cells of the adrenal cortex was reduced in different animals. The adrenal cortex of weanling rats placed on a panothenic acid deficient diet were observed by Deane and McKibbin, (1946) to be enlarged. Moreover, the zonal reticularis and fasciculata were progressively drained of ketosteroids and gave cytological evidence of exhaustion. By the end of 6 weeks, the zona fasciculata was entirely depleted of its hormone. The thymuses of these rats were atrophied in comparison with those of the control. These authors concluded that panothenic acid deficiency acts as an alarming stimulus for the rat. A thiamine deficiency in pigeons was found by Korenchevsky, (1923) to cause adrenal hypertrophy, thymus regression, and splenic regression. Injections of ACE into guinea pigs on a vitamin B_1 deficient diet reportedly improved the growth curve and delayed the onset of other deficiency symptoms (Lockwood and Hartman, 1933).

The role of the adrenal in sodium metabolism is well known. No attempt will be made to consider the vast quantity of work concerning this relationship. But as a matter of passing interest, it will be mentioned that administration of 0.9 per cent sodium chloride to

chickens for 17 days caused a 22 mm. increase in systolic pressure and a 9 mm. increase in diastolic blood pressure (Anonymous, 1949). Cessation of NaCl administration resulted in a return to normal which was found to be 132 mm. Hg. systolic and 117 mm. Hg. diastolic. The high normal diastolic pressure seemed to be related to its high body temperature. Selye, (1943) reproduced the symptoms of blue-comb disease in fowls by administering excessive doses of sodium chloride. This investigator proposed that in many instances, the spontaneous appearance of the disease may result from the ingestion of excessive sodium chloride. However, the writer believes that such an occurrence would be very unlikely where a commercial diet were used. There may be a remote possibility that "new grain" which has been reported to cause blue comb may contain some element exerting an effect similar to NaCl.

It was reported by Cullumbine, (1948) that NaCl solutions reduced the mortality rate of mice suffering from shock induced by immersion in hot water. This type of treatment was also effective in treating rats and rabbits suffering with mustard gas intoxication, but was not effective for goats. Reinhardt and Bloom, (1949) found that voluntarily ingested sodium chloride (1% in water) increased the lymph flow of rats to a volume 5 to 6 times greater than that observed in controls.

Stress stimuli have been observed to cause changes in the levels of blood sugar and body glycogen. These changes, as will be shown, seem to be associated with the activity of the adrenal. A marked increase in blood sugar was observed in cats by Smith and Oster,

(1946) after exposure of these animals to low oxygen tension. Insulin was found to decrease resistance to hypoxia and at the same time decreased post-hypoxic hyperglycemia about one-third. Evans, (1934) found a substantial increase in the total carbohydrate of rats when they were placed without food at one-half atmosphere for 24 hours. The greatest increase occurred in the liver and could not be accounted for by decreases in carbohydrate elsewhere. It was concluded that these observations may have resulted from the interconversion of either protein or fat to carbohydrate in excess of oxidative needs. This conversion seemed to be dependent on the presence of some adrenal tissue. Strand and Gordon, (1950) reported that adrenalectomy of female rats results in lowering of the glycogen content of the thymus, lymph nodes, spleen, as well as the liver. The respiration of these organs was found to increase following adrenalectomy; a change which could be reduced with ACE injections. It was shown by Kottke, et al (1948) that two commercial preparations of ACE and also desoxycorticosterone acetate injected subcutaneously were without beneficial effect to mice exposed to high altitudes. An aqueous extract of the adrenal prepared by Kendall when injected at levels greater than 0.25 cc. per mouse seemed to have beneficial effects, which were comparable with intraperitoneally injected glucose. The work of Ingle and Lukens, (1941) revealed that fatigue in the adrenalectomized rat could be reversed by injections with glucose, sucrose, and sodium chloride. Rats in this study were made to work immediately following adrenalectomy by stimulating the gastrocnemius muscle to

lift a 100 gram weight 3 times per second until muscular responsiveness was almost lost. Intravenous administration of glucose, sucrose, and sodium chloride caused an improvement in work output. Glucose had the most pronounced effect.

The nutrient, water, also has an important function in the animals adaptation to conditions of stress. A lack of water has been shown by Nichols, (1949) to have a significant effect on the adrenals of rats. A marked depletion of total lipids and especially of cholesterols was found in the adrenal cortices of animals exposed to prolonged dehydration (8 to 12 days). This depletion was especially pronounced in the zona fasciculata and the zona reticularis. The zona glomerulosa was the last to become depleted of lipids. Esposito, (1952) reported that a short period of water deprivation (24 hours) reduced the quantity of DFP (di-isopropylfluoro-phosphate) necessary to cause death when injected into mice.

Gravity shock was shown by Cole, et al (1944) to cause a suppression of urine flow in rabbits. It was found by Howlett and Browne, (1940) that gastric and intestinal manipulation and histamine injection resulted in a marked water restriction and edema formation. The degree of water retention was correlated with the intensity of damage. Previous work by these investigators (1937) had suggested that the disappearance of edema in the alarm reaction is facilitated by an increased output of cortin from the adrenal. Doses of cortin failed to affect water after surgical trauma in the intact animal nor did cortin affect the rate of water excretion in adrenalectomized animals otherwise undamaged. However, cortin did markedly

increase the rate of water excretion in adrenalectomized animals after surgical trauma or injection of histamine. Silvette, (1943) found that rats placed at simulated altitudes of 15,000 feet showed a 150 per cent increase in urine output and 25,000 feet caused a 300 per cent increase. These observations were made during a period of 3 hours. The polyuric response was sustained throughout the 27 days of the experiment. Urinary flow soon returned to normal within a few days when the animals were again placed at sea level.

This high altitude polyuria was further increased by cold, but decreased by heat. In the experiments of Stickney, et al (1946) anesthetized dogs were subjected to various degrees of anoxia (14, 11, 9, 7, and 5% oxygen in nitrogen). These investigators concluded that a mild anoxia produced an obliguria, but the incidence of either was affected by the type of anesthetic agent used. It was also shown by Stickney, (1946) that rats held at 28,000 feet altitude for 3-1/2 hours displayed increased urine secretion. During cold diuresis the specific gravity and chloride concentration of the urine was noted to fall as the volume rose (Bader, et al, 1949). Each change appeared to be correlated with the previous state of hydration and chloride content of the diet. The cold diuresis was inhibited by intramuscular injections of pitressin. Sargent and Consolazio, (1951) concluded that ketonuria (urine of soldiers) tended to be more common in cold climates than in temperate climates. The ketonuria was independent of the composition of the food consumed and of caloric expenditure.

THYROIDS - A close relationship has been shown to exist between the adrenal glands and the thyroids by a number of investigators. When animals are fed thiouracil, there is a rapid and progressive atrophy of the adrenals (Baumann and Marine, 1945; Deane and Greep, 1947; Zarrow and Money, 1949; and Freedman and Gordon, 1950). Surgical thyroidectomy of male rats was observed by Freedman and Gordon (1950) to produce a less pronounced adrenal atrophy but a greater adrenal inhibition as revealed by the final decrease in adrenal ascorbic acid concentration. These researchers found that the effects of both types of induced hypothyroidism on the adrenals could be prevented with thyroxin. The atrophy of the adrenal seems to be confined to the adrenal cortex because it was shown by Marine and Baumann (1945) that the adrenal medulla hypertrophies in rats fed thiouracil. Baumann and Marine, (1945) noted that there was frequently extreme congestion and hemorrhage in the reticular zone of the adrenals in rats fed thiouracil. This zone was found necrotic and scarred in the adrenals of cats fed thiouracil for prolonged periods. (McClosky, et al, 1947)

There has been some indication that hormones from the adrenals have a direct influence on the activity of the thyroids. Desoxycorticosterone was found by Parker, (1947) to counteract the retardation of tooth eruption and the opening of the eyelids cause in baby rats with thiouracil injections. Williams, et al (1949) concluded that adrenalin increased the rate at which thyrotropin is released from the pituitary. Similarly, Reiss, et al, (1949)

proposed that certain adrenal cortical hormones facilitate the release and/or the action of thyrotropin. These investigators observed that the uptake of I^{131} was increased four-fold in patients with Addison's Disease who received certain adrenal cortical extracts. In contrast, Paschkis, et al (1950) reported that desoxycorticosterone and ACE failed to influence thyroid uptake of I^{131} significantly, although a slight increase was noted.

The spleens of thiouracil fed rats have been found to shrink to 1/4 to 1/2 normal size (Baumann and Marine, 1945). Leathem, (1945) reported that a rise in total plasma protein occurred in rats fed 1 per cent thiourea for 20 to 22 days. This total protein rise was due entirely to an increase in plasma globulin, while the plasma albumin concentration did not change.

The effects of hyperthyroidism are opposite in some respects to hypothyroidism. Maqsood, (1951) reported that the administration of thyroxin to rabbits caused a significant increase in the weight of the adrenals. It was found by Wallach and Reineke, (1949) that hyperthyroid rats showed a decrease in ascorbic acid which reached a minimal value after 4 days of thyroxin administration. This period was found to be followed by a progressive increase in adrenal weight and ascorbic acid content which reached a maximum at 4 weeks. Following this period, there was a general leveling off during the fifth and sixth weeks. These investigators reported that the adrenals of these rats showed an increased secretion rate which was estimated to be between 10 and 20 dog units of adrenocortical hormone. It was concluded that the adrenals are discharging increased amounts of

cortical hormone in the blood stream during the early stages of induced hyperthyroidism if the vitamin C content is an index of secretion. Deane and Greep, (1947) found that during hyperthyroidism, the zona fasciculata of the cortex hypertrophies; with its ketosteroid content becoming at first augmented and subsequently depleted. There was abundant sign of cell death appearing in the inner fasciculata, while the zona glomerulosa became exhausted of ketosteroids. These workers proposed that there was an increased output of ACTH in hyperthyroidism.

Thyroxin also seems to augment the growth of the lymphatic organs. Marder, (1949) found that thyroxin caused an increase in the organ weights of the kidneys, spleen, and peripheral lymph nodes of mice. Similar treatment of adrenalectomized animals resulted in an increase in the weights of the spleen and peripheral lymph nodes over and above that which followed adrenalectomy alone. It was concluded that thyroxin produced an increase in lymphoid tissue mass which is independent of the rate of body growth and the level of adrenal cortical activity. There was a slight decrease in the thymic weights of intact animals treated with thyroxin in this study. Pentz, et al, (1950) reported that rats fed with desiccated thyroids had enlarged adrenals and atrophied thymus glands. Yet thyroid-fed groups which received liver supplement or vitamin B_{12} had hypertrophied adrenals, but this hypertrophy was not accompanied by thymic atrophy equivalent to that present in groups fed thyroid alone.

The thyroids by virtue of their control over metabolism and both the cortex and medulla of the adrenal gland have been designated as

the most important non-neural accessory thermoregulatory mechanism. It was reported by Hoffman and Shaffner, (1950) that the thyroid weights and metabolic rates of 7-week-old New Hampshire cockerels were increased following a 3-week exposure to cold. This response of the thyroid to conditions of cold is apparently not an immediate one. The research of Leblond, et al (1943) indicated that there was no definite change in the use of radioactive iodine during the first 3 days that rats were exposed to cold. Following this period, however, there was a progressive increase in the consumption of this substance; the maximum rate being reached at 26 days. Continued exposure for 40 days caused consumption to return toward the control level. Zarrow and Money (1949) observed a marked relationship between the size of the adrenal cortex and the resistance of 5-week-old rats to cold. Thiouracil treated rats were less able to withstand cold. No adrenal hypertrophy was noted in thiouracil treated rats after exposure to cold.

GONADS - It is probably true that no gland or organ of the living organism functions completely independent of any other gland or organ, but data has been obtained by several investigators which indicate the existence of a definite relationship between the gonads and the adrenals. The results of Herrick and Torstveit, (1938) revealed that the testes of White Leghorns regressed in size following adrenalectomy. Histological examination showed that the tubule walls were so broken down that the lumina were obscured. These observations lead the workers to conclude that the adrenal glands have an important function in maintaining the testes of chickens. Administration of

ACTH to male rats was observed by Baker, et al (1950) to cause a slight reduction in gonad weight. The treatment also resulted in an atrophy of the Leydig cells in about 80 per cent of the instances. Under conditions of stress, the testes have been shown to become smaller than normal. Tornetta, et al (1943) reported that male rats which had been exposed to altitudes of 25,000 to 28,000 feet for 6 hours each day for 14 to 18 days had smaller testes, seminal vesicles, and prostates. It was found by Altland, (1949 a, b, c) that daily exposure of rats to altitudes of 25,000 feet for prolonged periods of time caused a significant reduction in the reproductive capacity of both sexes. Exposure seemed not to affect the descent of the testes, but did cause a delay in the onset of puberty; and spermatozoa were late in appearing. The vaginal orifice of exposed females was from 1 to 6 weeks late in opening. Testes/body weight of these animals were 10.5 to 52.0 per cent less than the controls with the occurrence of severe disintegration of the seminiferous tubules resulting in some cases. The ovary/body weights ratios were less than controls during the period of exposure from 38 to 140 days after which the difference was not significant. Pregnancy occurred, but no live offspring were born. The author felt that this inability on the part of the female to reproduce was not due to a failure of the reproductive system; but rather to a general debility caused by the prolonged exposure to anoxia. Selye, (1950) proposed that under conditions of stress that there is a "shift in anterior pituitary production". According to this supposition, the pituitary releases reduced quantities of such hormones as gonadotropin, thyrotropin, etc.

when conditions demand the secretion of large quantities of ACTH. In a review by Christian, (1950) it was proposed that exhaustion of the adreno-pituitary system subsequent to the stresses inherent in a high population level, severe climatic conditions, and the demands of the spring breeding season may be responsible for the cyclic declines in population for a number of mammals.

The male hormone apparently exerts an influence on the adrenal. Peczenik, (1944) found that the reduction in adrenal weight in male hamsters following castration could be partially or completely alleviated with injections of the male hormone. In contrast, the adrenals of castrated females became larger and this effect was augmented by injections with the sex specific hormone. Testosterone propionate was reported by Leathem, (1944) to partially maintain the adrenal weights of hypophysectomized immature male rats. As the length of the injection period was extended (beyond 15 days) decreased adrenal weights occurred in spite of treatment with the male hormone.

Selye, (1940) observed that androgens such as testosterone or Δ^5-dehydro-iso-androsterone caused an involution in the adrenal cortex. This effect was more pronounced in the females than in the males. This investigator and co-workers (1943) reported that chronic treatment with large doses of methyl-testosterone resulted in a number of histological changes in the adrenal cortex of the male albino rat. Specifically, there was an involution of the glomerulosa, a marked thickening of connective tissue, with a deposition of coarse fat granules in the cells of the fasciculata and reticularis. In a study conducted by Longley, (1942), it was shown that

treatment with testosterone propionate apparently increased the survival rate of rats poisoned with small doses of mercuric chloride, but was without effect when larger doses of the poison were used.

NERVOUS SYSTEM - No attempt will be made in this review to give an extensive consideration to the nervous system. Unfortunately, the nervous system has been grossly neglected by investigators of the adaptation syndrome. A few interesting studies will be cited, however, in order to place the subject in some perspective.

The importance of ACTH in the stress response has already been emphasized. Hoagland, (1949) conducted an interesting study which lead him to the conclusion that ACTH secretion was associated in some manner with schizophrenia. Among normal individuals, it was found that the greater the stress, the greater was the secretion of this hormone. In contrast, schizophrenics displayed an inability to respond with enhanced output. It was observed by Gordon, (1950) that the discharge of adrenal ascorbic acid which normally results in rats following a fracture or a mild scald, was diminished if the leg had been denervated previously. With more severe scalds, denervation had no effect. Vogt, (1944) concluded that the sympathetic nervous system has an indirect control over the adrenal cortex which is mediated through adrenalin.

Neither stress nor adrenalectomy consistently changed choline acetylase or coenzyme level of brain tissue of rats in studies conducted by Greenberg, (1949). Hoagland and Stone, (1948) found that muscular fatigue induced by prolonged swimming caused a 4.4 per cent

reduction in brain potassium. A similar reduction was noted in the muscle tissue.

Evidence was presented by Grenell and McCawley, (1947) which indicated that ACE protected the cerebral cortex against structural and functional abnormalities caused by exposure. It was shown by Woodbury and Sayers, (1950) that rats treated with ACTH (1 mg., 3 times daily) experienced a slight decrease in the electro-shock seizure threshold which was followed by a return to normal and subsequently a slight increase in threshold. Cortisone administered in dose of 1 mg. twice daily markedly reduced the threshold. The anaerobic glycolysis of the rat brain is reduced to a level 20 per cent below normal after hypophysectomy, according to the results of Abood and Koosis, (1950). Anaerobic glycolysis was restored to normal by the administration of ACTH. Castor, et al (1951) reported that ACTH resulted in chromatolysis in the cells of the paraventricular hypothalmic nucleus. Cortisone also affected this nucleus but caused more widespread chromatolysis and vacuolation of thalmic and hypothalmic nerve cells.

MATERIALS AND GENERAL PROCEDURE

The New Hampshire and White Leghorn chickens used in this study were maintained in wire batteries from the time of hatch until they were sacrificed at the end of the experimental period. Prior to being placed on experiment, they were provided a standard broiler ration and water ad libitum. During certain experimental trials, this ration was modified by the addition of other substances which will be indicated where appropriate.

The factors considered in preparing comparable experimental and control groups depended upon the type of study being planned. If the age of the birds permitted sex identification, as it did in most instances, the control and experimental groups contained the same number of males and females. When observations were made using randomly selected normal chickens, body weight was also considered in formulating the groups. However, weight was not considered when preparing groups for studying the genetic aspects of the problem. In some experimental trials, the birds were divided into comparable groups on the basis of the time required to induce muscular fatigue; this observation being made prior to actually placing the birds on experiment.

The age of the birds used in most instances ranged from 3 to 6 weeks. An exception to this practice was the one-week-old birds used in a study planned to determine the level of cortisone causing toxicity.

The nature of stress considered during the study was essentially of 5 types: muscular fatigue, cold, high altitudes, emotional strain

and drug administration.

Muscular fatigue was induced by means of a revolving cage constructed by the author (fig. 1). This cage was 11.4 inches in diameter, giving it a circumference of 36 inches. Quite early in the study, it was necessary to construct 2 additional cages which are shown in figure 2. The speed of the revolving cages was regulated by tape pullers which were powered by 1/30 horsepower electric motors. As is seen in figures 1 and 2, the cages were equipped with timers. These were essential because of the types of studies conducted with the cages. One series of studies was of the type in which the birds were exercised until they fell exhausted on the floor of the cage, therefore, the time required to induce muscular fatigue was the foremost factor of concern. In other studies, the birds were exercised for a definite period of time. The revolutions per minute (r.p.m.) used in all studies herein described varied from 4 to 22. When the birds were exercised for a definite period of time, the lower r.p.m. were used, while higher r.p.m. were used in studies designed to induce muscular exhaustion. In all trials where the birds were exercised until exhausted, no bird was exercised more than once during a given 24 hour period.

Birds were exposed to cold by placing them in a walk-in type cooler which was maintained at 38° to 40° F. This room was equipped with batteries divided into cages large enough for two 6 to 8 week-old birds. During the experimental period, the room was lighted. The control groups of birds were kept in batteries at room temperature (approximately 75° to 80° F.).

Figure 1. The revolving cage used for inducing muscular fatigue.

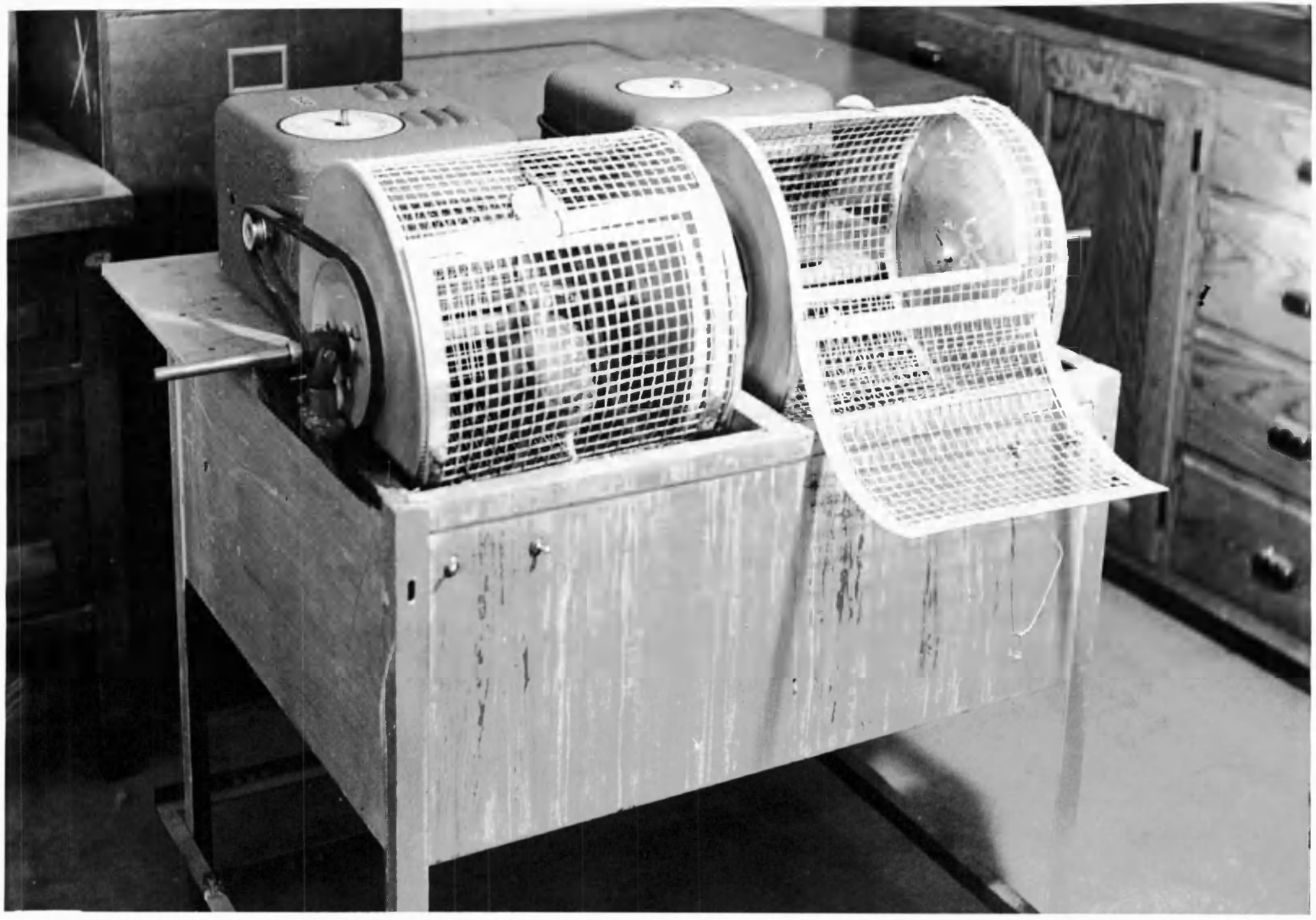

Figure 2. Two additional cages constructed for inducing muscular fatigue.

The apparatus used for simulation of high altitudes is shown in figure 3. It consisted of a large vacuum desiccator connected to a vacuum pump. The floor of the desiccator consisted of a perforated porcelain disc about 78 square inches in area. Air was drawn from the top of the desiccator and fresh air was admitted through a tube at the bottom. The negative pressure within the system was measured by a mercury column. In the studies of this type of stress, simulated altitudes of 12,000 to 15,000 feet were used. These experiments were conducted at room temperature (75° to 80° F.). A precision gas meter was used to determine the rate of air intake, which was found to be several times greater than the minimum required.

The aspect of emotional stress was not dealt with to any great extent, but in the study involving its use, it was induced by tying the birds securely to a frame covered with hardware cloth (see figure 4). The birds were bound loosely with wide rubber bands with one band attached to both wings which were first folded over the bird's back, and the other band was attached to both legs. To these bands were attached small hooks which were placed into the hardware cloth. In this manner the birds were held securely with a minimum of injury.

At the end of a given study, the birds were sacrificed by severing the blood vessels of the neck. Following death, the birds were autopsied and a number of observations were made. The lymphatic and endocrine glands were the main objects of consideration. These glands were weighed and those considered one or more times in the various studies reported were the pituitary, thymus, thyroid, adrenal, spleen, and bursa of Fabricius. The smaller glands, those weighing

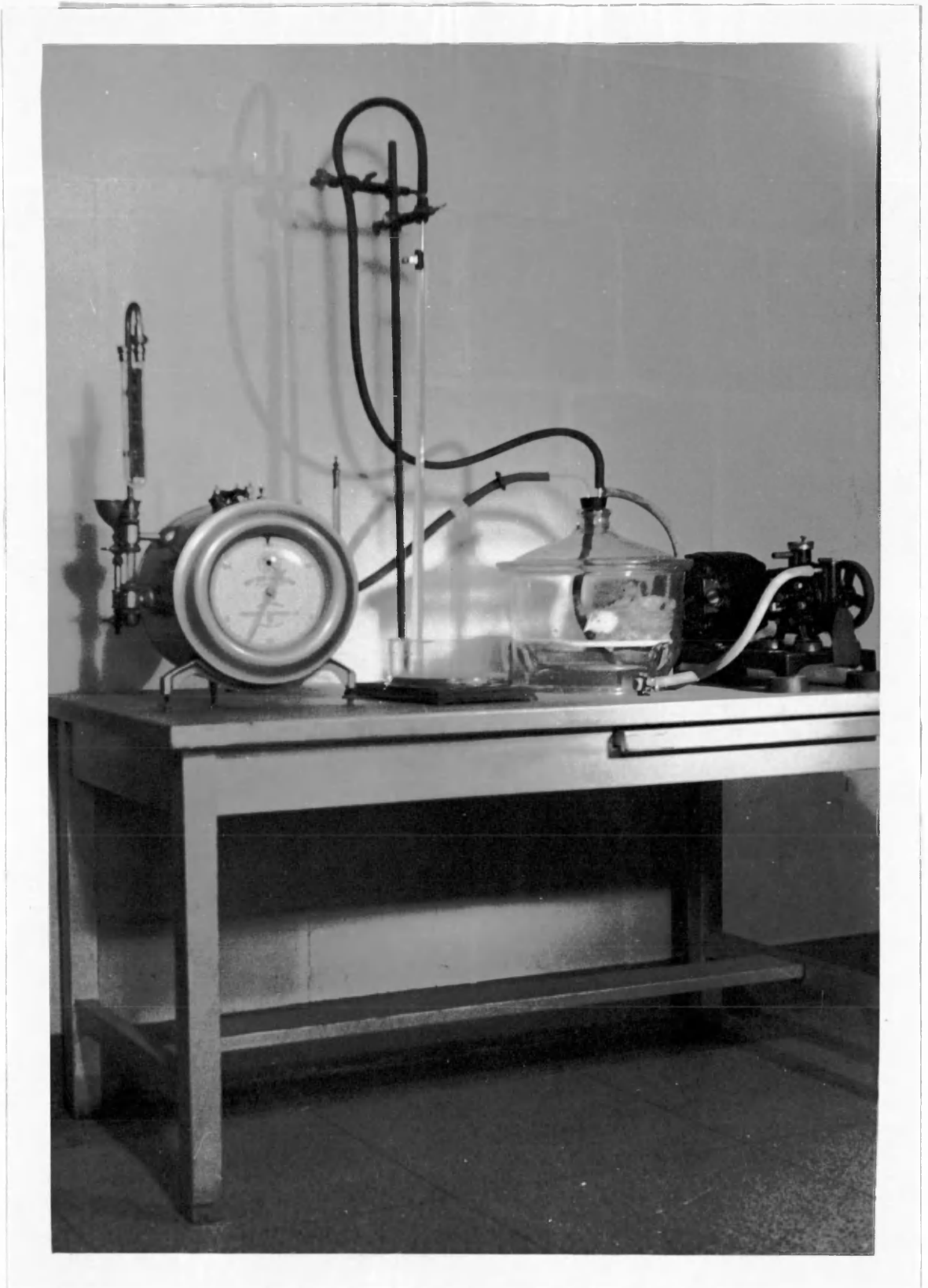

Figure 3. The apparatus used for the simulation of high altitudes.

Figure 4. The method of inducing emotional strain. The legs and wings of the birds were bound with rubber bands and hooked into the wire screen.

less than 500 mg., were weighed to the nearest 0.2 mg. on a Roller-Smith torsion balance. Those glands weighing more than 500 mg. were weighed on a conventional triple beam balance to the nearest 0.01 gram.

Removal of the glands was by a standard procedure in most instances, but the method employed for the removal of certain ones will be given in some detail. Needless to say, all the tissues weighed were cleaned of exogenous material prior to weighing.

The removal of the pituitary was as follows: First the lower mandible was removed. This first step was found simpler if performed on all the birds at the time they were killed. With a dissecting scalpel, the fleshy portion of the oral cleft was scraped away, exposing the region between the occipital bone and the sphenoidal rostrum. At this point a triangular cut was made in the bone as is shown in figure 5. This freed flap of bone was then caught underneath the anterior edge and flipped posteriorly, care being taken not to disturb the brain tissue below. Once the bone has been removed, the gland is usually found near the anterior junction of the triangle. Using the blade of the improvised instrument shown in figure 6, the membrane surrounding the gland was cut and the gland was carefully removed with the pointed forceps. Occasionally, especially in older birds, the pituitary was found to cling to the pituitary fossa found in the bony flap which was removed. When this was the case, it was necessary to carefully pick the gland from its location with a hooked dissecting needle or to pick away the bone from around it with the fingernails.

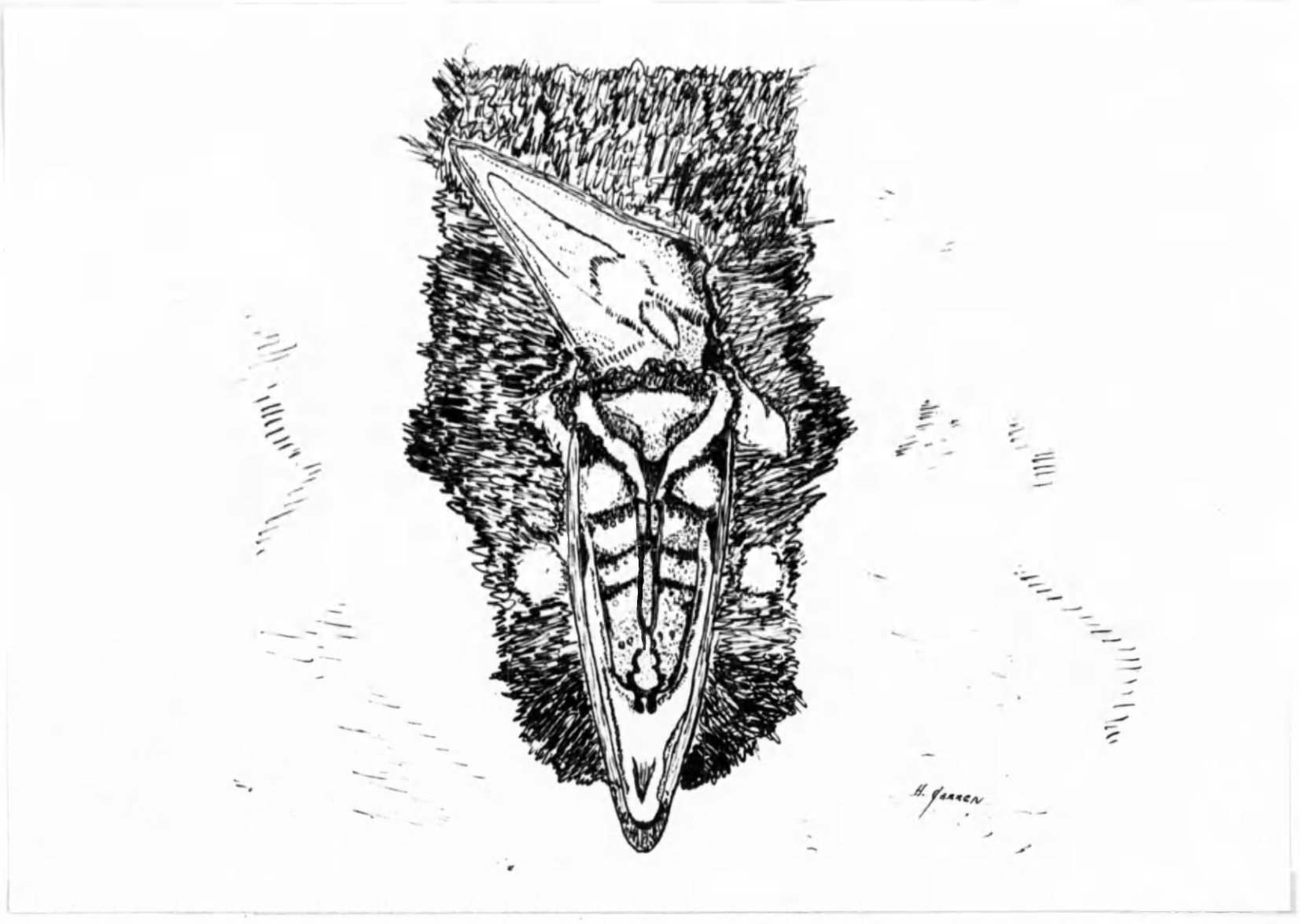

Figure 5. The location of the triangular cut made between the occipital bone and the sphenoidal rostrum for the purpose of exposing the pituitary.

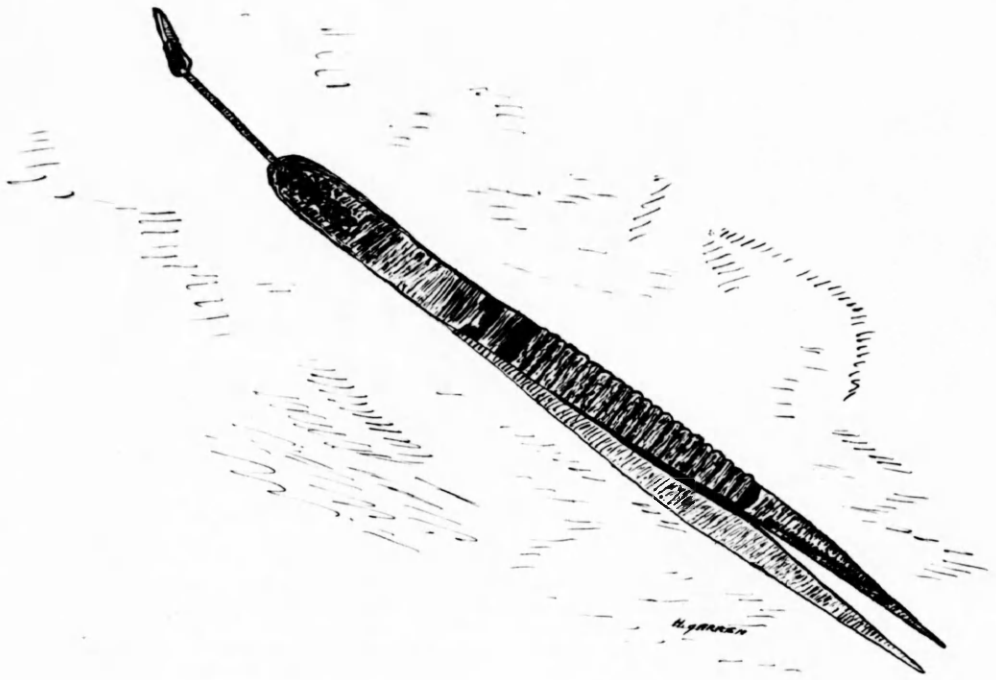

Figure 6. The instrument developed for the purpose of facilitating the removal of the adrenals and the pituitary.

The latter procedure, though often more time consuming, was found more desirable because of minimum damage to the gland. Following removal, the gland was weighed.

Before removing the remaining glands, it was necessary to open the bird. The procedure used to accomplish this end was one which is quite common in poultry-autopsy laboratories. First the bird was placed on its back and the skin between the legs and the torso was severed. Each leg was then folded flat on its respective side. The skin was firmly grasped about midway of the abdominal cavity and pulled anteriorly. An incision was made in the abdomen and continued along each side of the bird just below the pectoral muscles. The entire breast was folded forward and worked loose from the carcass. This method of autopsy was found to expose all the considered glands to the best advantage. A completely autopsied bird is shown in figure 7.

The thymus tissue was removed by splitting the skin of the neck and folding it toward each side. The areas of thymus were stripped from the adhering membranes, carefully cleaned and weighed.

Removal of the thyroid is such a simple matter that the procedure need not be resolved here. The two glands were merely cut from their location along the carotid artery.

The adrenal glands of the chicken are quite difficult to remove without shattering. The first step in their successful removal is the elimination of the gonads. In the male this is easily accomplished by pulling each testis from its location with forceps. Removal of the female gonad without damaging the adrenals presents a more difficult

Figure 7. A fully autopsied bird showing the glands and organs considered during the study.

problem since the ovary of the young bird is in close association with the gland. It was found that by using a sharp dissecting scalpel that the gonad of the female could be literally shaven from the adrenal.

Once the gonads have been disposed of, the way is clear for the removal of the adrenals. This was best accomplished by using a specially improvised instrument, shown in figure 6. The instrument consisted of sharp-pointed forceps with a bit of broken razor blade attached to the stationary or base end. By means of solder, the blade was first fastened to a steel needle which was then soldered to the forceps. A great deal of time was saved by having both the dissecting blade and forceps combined in one instrument. The blade was sharpened from time to time by means of a leather hone.

The actual removal of the adrenal consisted of patiently cutting around the periphery of the gland with the small blade, gradually working underneath the gland. Once the gland had become sufficiently loosened, it was removed by grasping it with the forceps. After cleaning away the excess material, it was weighed.

The bursa of Fabricius, which is a lymphatic gland in the region of the cloaca, was found to be rather resistant to removal by instruments. This gland is very tender and requires only a small amount of carelessness to be torn. It was found that a long fingernail on the forefinger was the best tool for its removal. By carefully working the nail underneath and around the gland, it was easily freed from the adhering membranes.

Additional procedure will be described where essential or desirable.

RESULTS

The following presentation of results treats the present study in four distinct phases. Phase I includes those trials designed for the purpose of observing a fowl's response to muscular fatigue. This phase of the study investigated such factors as the fundamental anatomical changes in the stress-response, possible genetic differences involved, and attempts to enhance the fowl's resistance to fatigue, with exogenous hormonal therapy. Phase II considered the response of the fowl to stress in the form of cold. Basically the study was one of a time relationship; that is, it was an attempt to determine the morphological state of various glands as apparently influenced by time of exposure to cold. However, a rather limited investigation was also made into the genetical variations of response in two strains of fowl. Phase III was an attempt to establish the shortest period of exposure to stress necessary to elicit a discernible weight change in such glands as the adrenals, pituitary, bursa of Fabricius, and spleen. The various forms of stress employed were those of muscular fatigue, high altitudes, cold and emotional strain. In Phase IV of this study, the degree of stress-response induced by either thiouracil or protamone administration for varying periods of time was elucidated.

The several forms of stress used were not considered without purpose. The author concluded from his search of the literature that the clearest understanding of the stress phenomena in chickens should be acquired through the use of a number of different stress stimuli, applied in a number of different ways. It is believed that the results

of this study bear out the validity of this conclusion.

Because of the large volume of data involved, no attempt has been made at this time to make a complete statistical analysis. Where the gland weights are given, they are presented as average values with the standard errors. In most cases, these values are given for the males and females of both the experimental and control groups. It was believed that more informative results could be secured by treating the sexes separately. Of course, in the instances where the males and females have not differed markedly, the standard errors obtained for the gland weights of each sex are larger than would be obtained if the sexes had been considered together. This thought should be borne in mind by the reader in considering the results of the various experiments.

PHASE I

Muscular Fatigue Study

Trial 1

This study was designed in such a manner as to make it essentially exploratory in nature. It was desired in this experiment to determine the rather general effects of exposing the birds to muscular fatigue over an extended period of time. For this purpose, two comparable groups of New Hampshires 32 days of age were selected with each group containing 6 males and 6 females. During a period of 10 days, each bird of the experimental group was exercised 4 times with the cages shown in figures 1 and 2 turning at a rate of 12 r.p.m., 3 times at 17 r.p.m., and 3 times at 22 r.p.m. At the termination of this period, both the experimental and the control group were sacrificed, and the weights of the following glands and organs were taken: pituitary, thyroid, adrenal, gonads, thymus, bursa of Fabricius, pancreas, liver, spleen, kidney, heart, and comb (male). In addition to these measurements, live body weight and feed consumption were also considered. Furthermore, the proventriculus (stomach) and the duodenum were examined for signs of irritation.

In order to illustrate the extreme variation in the apparent resistance of this strain of New Hampshires to fatigue, the actual revolutions required to exhaust each bird of the experimental group are given in Table I. From these data it is seen that most birds

TABLE I

THE NUMBER OF REVOLUTIONS REQUIRED TO EXHAUST THE EXPERIMENTAL BIRDS EACH TIME THEY WERE REVOLVED

(Trial 1)

	12 r.p.m.					17 r.p.m.			22 r.p.m.		
Day	1	2	3	4	5	6	7	8	9	10	Average
Bird No.											
51*	30	70	114	199	255	223	68	251	112	260	158
52*	80	124	191	647	187	134	282	139	202	187	217
69*	67	82	146	434	153	330	840	319	198	315	288
82*	126	449	614	834	876	1416	1635	1588	1227	1762	1053
90*	240	394	1470	2302	325	415	581	348	469	561	710
95*	49	54	78	137	88	129	133	161	277	378	148
28**	18	40	59	89	137	139	133	114	119	183	98
33**	262	155	608	778	371	724	748	279	352	616	490
54**	41	88	210	161	160	80	301	165	183	97	148
71**	58	119	534	1985	413	1520	5875	1410	4871	8268	2505
87**	36	71	97	114	75	116	162	145	143	167	113
94**	31	334	334	736	689	1579	3057	605	565	660	858

*males
**females

seemed to become progressively more resistant to fatigue as the study was continued. There was an indication that the calm, docile individuals could withstand the revolving for the greatest period of time. Frequently, it was noted that the droppings of birds became watery while they were being revolved in the cages. This condition became especially evident on the third or fourth day of the study and was most pronounced in the birds requiring the longest period of time to exhaust. Soon after the birds were returned from the revolving cages to the batteries, watery droppings were no longer observed. As noted in Table II the experimental birds consumed slightly less feed than the control group. The former group also gained less weight than the control during the experimental period.

An examination of the autopsy data in Table II reveals that certain of the various glands and organs considered are morphologically different for the experimental group. The adrenal glands of this group were heavier, but the variation in the weight of these glands was also pronounced. Those individuals requiring the greatest number of revolutions to exhaust were also found to have the largest adrenal glands. Bird 71 shown in Table I was the most resistant individual of the trial. This bird had a relative adrenal weight of 19.14 mg., which was 5.24 mg. heavier than the average for the experimental group. However, a close correlation was not found to exist between the revolutions required to exhaust these birds and their adrenal weights. Among the birds showing rather high resistance to fatigue, a correlation of this nature was suggested. But the adrenal weights of the birds with low resistance seemed to bear no relation-

TABLE II

THE AVERAGE WEIGHTS OF THE GLANDS AND ORGANS CONSIDERED

(Trial 1)

Gland or Organ	Weight in mg./100 gm. of body weight CONTROL GROUP	 EXPERIMENTAL GROUP
Pituitary	0.98 ± 0.04	1.20 ± 0.08
Thyroid	7.22 ± 0.50	6.21 ± 0.64
Adrenal	11.40 ± 0.69	13.90 ± 0.80
Thymus	719.7 ± 45.5	512.6 ± 42.9
Bursa	520.8 ± 45.6	365.9 ± 23.5
Gonads	31.5 ± 3.6	27.3 ± 1.8
Spleen	237.0 ± 10.7	232.0 ± 18.9
Kidney	893.4 ± 25.5	963.9 ± 41.8
Comb (6 males)	216.6 ± 40.0	197.1 ± 35.2
Heart	547.7 ± 16.9	669.7 ± 24.1
Pancreas	304.7 ± 11.6	324.4 ± 18.5
	Weight in gm./100 gm. of body weight	
Liver	2.53 ± 0.06	2.56 ± 0.11
	Body Weight in Grams	
Initial	393	399
Final	568	522
	Feed Consumption in Pounds	
Control	11.0	
Experimental	10.5	

ship to the revolutions required to cause exhaustion.

The thymus glands and the bursae of the experimental chickens were much lighter in weight than those of the control. These glands were found to be the smallest in the birds showing the greatest resistance to fatigue.

Slight increases in the weights of the pituitaries, pancreas, kidneys, and hearts were also noted for the birds of the experimental group. On the basis of absolute weight, the pancreas and kidneys were not different from those of the control birds. Of course, the standard errors for the weights of both glands are quite large.

The liver and spleen weights of the experimental group were similar to the weights of these glands for the control group.

The weights of the thyroids, gonads, and combs (male) were slightly less for the revolved group, but in these instances the variation was also large.

Birds number 33, 54, 90, and 71 listed in Table I had irritated areas about the size of a match head scattered throughout the duodenum. In addition, the proventriculus of number 71 possessed these areas.

Trial 2

This trial was conducted to determine if there were a discernible sex difference in New Hampshires with respect to their exhaustion revolutions. It was also thought that an additional investigation of a few of the foregoing observations might prove desirable. For this reason, the weights of the pituitaries, thyroids, adrenals, and bursae of the 10 males requiring the largest number of revolutions to exhaust were compared with the weights of these glands from the 10 males with the lowest resistance to fatigue. This same procedure was followed with the same number of females. The forty birds (20 males and 20 females) used in this study were 32 days of age. Over a period of 11 days, each bird was exercised until exhausted for 2 times at 12 r.p.m. 2 times at 17 r.p.m., and 3 times at 22 r.p.m.

It would seem that the males were more resistant to fatigue than the females according to the results presented in Table III. Evidence will be given in subsequent studies to support this observation. The bursae of the most resistant males and females were smaller than for the birds of each sex displaying the least resistance to fatigue (see Table IV). Yet for the other glands considered, there was no marked difference between the two groups of each sex. The adrenals of the males with the greatest resistance to fatigue were somewhat larger. It was found that the 2 males requiring the largest number of revolutions to exhaust had adrenal weights of 22.63 and 25.51 mg./100 gm. of body weight.

TABLE III

THE MEAN AND MEDIAN NUMBER OF REVOLUTIONS
REQUIRED TO EXHAUST THE MALES AND FEMALES
AT 12, 17, and 22 R.P.M.

(Trial 2)

	12 r.p.m.	12 r.p.m.	17 r.p.m.	17 r.p.m.	22 r.p.m.	22 r.p.m.	22 r.p.m.
AVERAGE:							
Males	97	628	374	887	585	770	1379
Females	103	208	139	184	187	194	238
MEDIAN:							
Males	65	155	112	349	284	174	246
Females	56	126	141	201	147	132	154
RANGE:							
Males	20-305	46-5796	70-3487	90-6120	66-2838	46-6930	57-15,070
Females	24-380	14-1013	32- 415	31- 435	44- 642	24- 876	51- 770

TABLE IV

A COMPARISON OF THE GLAND WEIGHTS FOR THE HIGH AND LOW RESISTANT BIRDS OF EACH SEX

(Trial 2)

	Weight in mg./100 gm. of body wt.			
GLAND:	High Males	Low Males	High Females	Low Females
Pituitary	1.06 ± 0.06	0.94 ± 0.05	0.96 ± 0.07	0.83 ± 0.08
Thyroid	6.72 ± 0.48	6.63 ± 0.37	7.24 ± 0.49	9.08 ± 0.55
Adrenal	15.51 ± 1.57	12.53 ± 0.36	12.66 ± 0.62	13.23 ± 0.66
Bursa	337.5 ± 32.8	439.4 ± 32.8	349.3 ± 18.8	457.7 ± 30.4
Initial Wt.	354 gm.	382 gm.	332 gm.	339 gm.
Final Wt.	546 gm.	598 gm.	509 gm.	521 gm.

Trial 3

In this trial, the exhaustion revolutions were determined for the offspring (New Hampshire) of a number of the dams constituting the high- and low-thiouracil-response strains of the farm flocks. A total of 92 offspring about 36 days of age were used. These were from 21 different dams and 6 different sires. On the basis of the thyroidal hypertrophy observed in the full siblings of these offspring, a given dam was designated as high or low with respect to thyroid hypertrophy following thiouracil feeding. The degree of thyroid hypertrophy in the siblings was determined by Mr. William E. Shaklee in conjunction with his research. Each individual was exercised twice at 12, twice at 17, and 3 times at 22 r.p.m.

In Table V are given the over-all average number of revolutions required to exhaust the offspring of each dam. Since these values were indicative of the differences seen to exist between the groups, they are given rather than the averages obtained at each of the r.p.m. used. Attention is directed to the observation that the two groups of offspring which required the greatest number of revolutions to exhaust were from high-thiouracil-response dams. Though the differences seemed pronounced, none of the differences were found to be significant. Unfortunately it was not possible to continue this study because the sires were mistakenly marketed.

TABLE V

THE OVER-ALL AVERAGE NUMBER OF REVOLUTIONS REQUIRED TO EXHAUST THE OFFSPRING OF 21 DAMS FROM THE HIGH- AND LOW-THIOURACIL-RESPONSE STRAINS

(Trial 3)

Sire	Dam	Number of Offspring	Revolutions Required to Exhaust	
			Mean	Range
1	A(low)*	2F.	44	34-54
	B(low)	2M., 1F.	89	53-159
	C(high)	3M., 1F.	1369	141-4111
	D(low)	3M., 4F.	548	43-2298
2	E(high)	2M., 1F.	199	81-330
	F(high)	2M., 4F.	166	64-312
3	G(high)	2M., 1F.	87	54-154
	H(high)	2M., 4F.	189	48-390
	I(high)	2M.	343	58-647
	J(high)	5M.	1776	60-6157
4	K(high)	2M., 2F.	309	86-459
	L(high)	3M., 4F.	287	99-468
5	M(high)	1M., 2F.	276	120-453
	N(low)	2M.	477	176-778
	O(low)	3M.	174	70-238
	P(high)	4M., 4F.	266	50-553
	Q(low)	1M.	121	
	R(high)	1M., 2F.	173	153-189
6	S(low)	4M., 4F.	353	101-676
	T(low)	2M., 2F.	143	86-214
	U(low)	3M., 2F.	101	64-159

* Indicates whether the thyroid hypertrophy of siblings from this mating was high or low following thiouracil feeding.

TRIAL 4

This study was undertaken to ascertain whether or not a discernible difference in resistance to fatigue existed between the White Leghorn and the New Hampshire. To make this observation, one group of New Hampshires was selected which consisted of 8 males and 8 females 33 days of age, and a similar group of White Leghorns was selected. Prior to commencing the study, the birds from which both groups were selected had been hatched together in the same hatching trays and had been raised together under the same environmental conditions. During the period of the experiment, a similar procedure was followed with respect to providing similar environmental situations for both groups. The individuals of each group were exercised twice at 12, 17, and 22 r.p.m. over a period of 10 days. In this trial as in other studies of this type, the individuals of each group were exercised in an alternate manner; e.g., New Hampshire, White Leghorn, etc.

Because of the extreme variation in the revolutions required to exhaust the birds of both groups as shown in Table VI, it cannot be said that there was significant difference between the two breeds of chickens with regard to resistance to muscular fatigue. As a group, the Leghorns were more resistant to fatigue than New Hampshires, but the two most resistant individuals of the study were New Hampshires. For this reason, the average revolutions required to exhaust the two groups have little meaning. However, it is seen in this Table that the median values are higher in all instances for the Leghorns. The

average gland and body weights for the two groups are given in Table VII. It is noted that the gland weights did not differ greatly except for the adrenals which were larger in the Leghorns. Of interest is the observation that the bursae were largest for the Leghorn females. It is also seen that the spleens for the females of each group were larger than those of the males. Of course, the average body weight of the Leghorns was less than for the New Hampshires.

TABLE VI

THE REVOLUTIONS REQUIRED TO EXHAUST WHITE LEGHORNS AND NEW HAMPSHIRES AT THE R.P.M. INDICATED

(Trial 4)

GROUP	Revolutions per Minute 12	12	17	17	22	22
White Leghorns:						
Mean Revs.	145	250	206	406	334	526
Median Revs.	70	148	184	274	293	297
Range	10-718	24-1180	48-512	95-1785	66-766	48-1408
New Hampshires:						
Mean Revs.	272	256	201	226	209	418
Median Revs.	60	106	88	131	124	169
Range	13-1934	28-1252	22-1037	36-1149	29-715	22-2299

TABLE VII

THE AVERAGE GLAND WEIGHTS FOR THE WHITE LEGHORNS AND NEW HAMPSHIRES WHICH HAD BEEN REVOLVED ON DIFFERENT DAYS UNTIL EXHAUSTED

(Trial 4)

GROUP	Weight in mg./100 gm. of body wt. Pitui.	Thyroid	Adrenal	Bursa	Spleen
White Leghorns:					
Males (8)	1.12 ± 0.05	5.62 ± 0.28	15.23 ± 0.54	390.4 ± 49.2	187.4 ± 9.3
Females (8)	0.91 ± 0.06	6.95 ± 0.44	14.82 ± 0.44	535.0 ± 50.5	250.7 ± 17.9
New Hampshires:					
Males (8)	1.00 ± 0.06	5.80 ± 0.35	11.79 ± 0.61	423.0 ± 42.7	172.0 ± 10.4
Females (8)	0.87 ± 0.05	6.57 ± 0.46	11.29 ± 0.99	405.9 ± 28.0	232.2 ± 10.4

	Body Weight, grams Initial	Finish
White Leghorns:		
Males	299	421
Females	269	377
New Hampshires:		
Males	385	579
Females	358	533

Trial 5

This study was planned for the purpose of comparing the exhaustion period of the turkey with that of the chicken. The turkeys used were from the farm stock, which had been developed from matings between Broad Breasted Bronze and Beltsville Whites. Both the turkeys and the New Hampshire chickens with which they were compared were raised together in the same wire battery. When they were 30 days of age, one group of turkeys and one group of the chickens was selected. Each group contained 8 males and 8 females. The individuals of both groups were exercised one time at 12 r.p.m. until they became exhausted after which they were autopsied.

When this study was planned, it was intended to revolve the individuals of each group several times until they became exhausted. However, the unusual resistance of the turkey to fatigue made this procedure physically impossible. From the results given in Table VIII, there can be little doubt that the turkeys required a much larger number of revolutions to exhaust than the chickens. When the turkeys were being revolved, they displayed practically no signs of excitement. Each individual calmly walked in the revolving cages until completely exhausted. As shown in Table IX, the average body weights were greater for the turkey than for the chicken. All the glands considered weighed relatively less for the turkeys, particularly the bursae and spleens. (Table IX)

TABLE VIII

THE REVOLUTIONS REQUIRED TO EXHAUST THE TURKEY AND THE CHICKEN AT 12 R.P.M.

(Trial 5)

GROUP	Number of Revolutions to Exhaust		
	Mean	Median	Range
Turkeys	2485	1495	202-4622
Chickens	214	96	19-1080

TABLE IX

THE AVERAGE GLAND WEIGHTS FOR THE TURKEYS AND CHICKENS WHICH HAD BEEN REVOLVED AT 12 R.P.M. UNTIL EXHAUSTED

(Trial 5)

GROUP:	Weight in mg./100 gm. of body wt.				
	Pitui.	Thyroid	Adrenal	Bursa	Spleen
Turkeys:					
Males	1.21 ± 0.08	4.88 ± 0.20	11.19 ± 0.92	175.4 ± 12.5	126.6 ± 9.3
Females	1.26 ± 0.13	5.77 ± 0.30	11.32 ± 0.78	186.5 ± 12.8	118.3 ± 12.8
New Hampshires:					
Males	1.39 ± 0.18	7.09 ± 0.35	15.68 ± 1.20	483.8 ± 67.3	272.4 ± 46.8
Females	1.40 ± 0.07	8.60 ± 0.84	15.31 ± 0.41	475.3 ± 25.3	367.1 ± 22.7

Trial 6

While the differences were not significant, there was an indication in trial 3 that the progeny from certain dams of the high-thiouracil-response strain possessed a marked resistance to muscular fatigue. It was therefore reasoned that there might be a relationship between the resistance of a bird to fatigue and the subsequent response of its thyroid to thiouracil administration. Three separate studies were conducted for the purpose of testing this hypothesis.

In the first study, the revolutions required to exhaust 45 birds 33 days of age was twice determined at 12 r.p.m. On the basis of the number of revolutions required for exhaustion during the second revolving, these birds were divided into 3 groups with 12 birds in each group (6 males and 6 females). A low exhaustion group consisted of birds requiring fewer than 48 revolutions to exhaust. The second or high exhaustion group contained birds requiring more than 180 revolutions to exhaust. The third or control group contained individuals which required between 50 and 150 revolutions to exhaust. For a period of 2 weeks, the first two groups were fed thiouracil at a level of 0.2 per cent. The control group was fed the same diet without thiouracil.

The second study was basically a repetition of the first. However, only one exhaustion period was determined at 12 r.p.m. for 126 birds 31 days of age. From these individuals, the following 3 groups of 24 birds (12 males and 12 females) were selected: (1) This group was made up of low exhaustion birds requiring fewer than 36 revolutions

to exhaust. (2) A high exhaustion group; the individuals of which required more than 120 revolutions to exhaust. (3) This group, the control, contained chickens requiring between 50 and 120 revolutions to exhaust. A diet containing 0.2 per cent thiouracil was fed to the first 2 groups for 2 weeks after which they were sacrificed. The control group received the same diet during this period, but without the thiouracil.

The third study was conducted in such a manner as to make it more nearly a repetition of the first study than was the second. The exhaustion revolutions of 80 birds 32 days of age were determined twice at 12 r.p.m. On the basis of the number of revolutions necessary to exhaust them during the second revolving, 3 groups of 16 birds (8 males and 8 females) were selected. The first of these constituted the low exhaustion group, each individual of which required less than 30 revolutions to exhaust. A second or high exhaustion group consisted of birds which had required more than 192 revolutions to exhaust. In addition, a third or intermediate exhaustion group was selected. Between 50 and 150 revolutions were required to exhaust each bird of this group. Prior to being sacrificed, all 3 groups were placed on a diet containing 0.2 per cent thiouracil for 2 weeks. The intermediate group was fed thiouracil in order to determine whether the response of this group to the drug was different from that of groups 1 and 2. All the chickens used in these 3 studies were New Hampshires.

There is very little information to be gleaned from the results of these 3 studies. In the first study there was an indication that the low exhaustion group subsequently displayed the greatest response

to thiouracil (Table X). It was not possible, however, to confirm this observation in the second or third studies. As a matter of passing interest, it might be pointed out that the bursae of the groups fed thiouracil in the first and second studies were markedly lighter in weight than those for the control individuals.

TABLE X

THE AVERAGE GLAND WEIGHTS OF THE LOW- AND HIGH-EXHAUSTION BIRDS AFTER TWO WEEKS ON THIOURACIL

(Trial 6)

GROUP	Weight in mg./100 gm. of body wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Init.	Final
Study 1							
Low Exhaustion:							
Males (6)	0.93 ± 0.10	28.45 ± 3.54	9.45 ± 0.85	252.8 ± 26.1	129.0 ± 5.3	417	774
Females (6)	0.77 ± 0.07	30.05 ± 5.06	7.35 ± 0.42	295.9 ± 25.2	184.9 ± 22.9	360	611
High Exhaustion:							
Males (6)	0.83 ± 0.09	19.77 ± 1.43	8.35 ± 0.57	258.3 ± 34.1	170.2 ± 18.3	403	708
Females (6)	0.76 ± 0.03	22.43 ± 1.64	10.13 ± 0.86	261.9 ± 25.3	156.9 ± 15.7	368	618
Control:							
Males (6)	0.73 ± 0.04	5.33 ± 0.55	9.67 ± 0.78	509.5 ± 55.7	180.4 ± 16.1	404	742
Females (6)	0.77 ± 0.04	7.14 ± 0.94	9.84 ± 0.57	473.6 ± 56.6	235.3 ± 15.5	375	673
Study 2							
Low Exhaustion:							
Males (12)	0.97 ± 0.06	19.19 ± 2.48	10.21 ± 0.49	310.9 ± 23.5	180.6 ± 9.15	--	652
Females (10)	0.97 ± 0.09	20.50 ± 2.75	10.81 ± 0.87	327.0 ± 37.4	208.3 ± 15.6	--	557
High Exhaustion:							
Males (11)	1.04 ± 0.04	20.43 ± 3.12	11.10 ± 0.55	261.2 ± 17.5	160.1 ± 12.2	--	650
Females (9)	0.92 ± 0.07	18.87 ± 2.20	9.45 ± 0.79	236.8 ± 28.0	197.5 ± 14.5	--	610

TABLE X, Cont'd.

THE AVERAGE GLAND WEIGHTS OF THE LOW- AND HIGH-EXHAUSTION BIRDS AFTER TWO WEEKS ON THIOURACIL

GROUP	Weight in mg./100 gm. of body wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Init.	Final
Control:							
Males (11)	1.01 ± 0.08	7.99 ± 0.72	11.85 ± 0.95	456.1 ± 27.2	200.2 ± 13.8	--	594
Females (12)	0.91 ± 0.06	9.65 ± 1.00	10.43 ± 0.60	498.0 ± 30.0	216.4 ± 20.2	--	522
Study 3							
Low Exhaustion:							
Males (8)	0.89 ± 0.09	33.88 ± 6.02	11.72 ± 0.82	201.4 ± 13.8	168.8 ± 25.9	330	704
Females (8)	0.91 ± 0.07	42.74 ± 6.88	9.79 ± 0.66	250.5 ± 25.1	195.0 ± 18.6	321	637
High Exhaustion:							
Males (8)	0.82 ± 0.07	38.83 ± 6.01	9.85 ± 0.49	260.8 ± 23.9	161.2 ± 13.8	351	762
Females (7)	0.75 ± 0.07	33.67 ± 6.38	11.06 ± 0.62	188.0 ± 15.6	153.1 ± 11.9	322	640
Interm. Exhaustion:							
Males (8)	0.81 ± 0.08	40.03 ± 4.67	10.66 ± 0.65	196.5 ± 28.8	145.8 ± 21.8	385	764
Females (8)	0.68 ± 0.04	28.60 ± 4.65	10.55 ± 0.83	240.0 ± 17.3	161.3 ± 13.9	--	--

Trial 7

It is common knowledge that a marked individual variation in thyroid weights exists among chickens which have been administered thiouracil. It was noted in a preliminary study that the individuals showing the greatest resistance to fatigue following a two-week period on thiouracil also had the largest thyroid glands. In this preliminary study, two comparable groups of 10 New Hampshires 26 days of age were selected. For a period of two weeks, one group was placed on a diet containing 0.2 per cent thiouracil, with the second group constituting the control. The pituitaries and thyroids of the experimental birds were larger, but the adrenals and bursae were smaller. The control birds required over twice as many revolutions to exhaust as the birds of the experimental group. The average thyroidal weights of the 8 individuals of the experimental groups, requiring fewer than 50 revolutions to exhaust, was 33.28 mg./100 gm. of body weight; compared with an average thyroid weight of 48.66 mg./100 gm. of body weight for the 2 males requiring 161 and 517 revolutions to exhaust. Therefore, the present trial was planned in which 50 New Hampshires (29 males and 21 females) 30 days of age were selected which had required in excess of 124 revolutions to exhaust during the second revolving at 12 r.p.m. These individuals were placed on thiouracil (0.2 per cent) for two weeks at the end of which time they were again revolved twice at 12 r.p.m. Those birds of each sex still requiring greater than 124 revolutions to exhaust were designated "high resistant" and those requiring fewer than 124 were designated "low resistant".

The results of this trial are shown in Table XI. It is seen that the thyroid weights of the most resistant males were about 2 times greater than the thyroid weights for the "low resistant" males. The thyroid weight for the most resistant individual male was 120.97 mg./100 gm. of body weight. This was the greatest thyroid weight observed in the trial. But for the females, there was no great difference in the thyroid weights of the two groups, though the thyroids were slightly heavier in the group with the greatest resistance. There was an indication that the adrenal weights for the "high" group of each sex were larger than for the "low" group.

TABLE XI

THE THYROID AND ADRENAL WEIGHTS FOR THE BIRDS OF EACH SEX SHOWING THE GREATEST AND LEAST RESISTANCE TO FATIGUE AFTER TWO WEEKS OF THIOURACIL (0.2%) FEEDING

(Trial 7)

GROUP:	Weight in mg./100 gm. of body wt.		Body Wt., Gms.	
	Thyroid	Adrenal	Initial	Final
High Males (10)	61.78 ± 9.26	11.08 ± 0.72	351	629
Low Males (19)	28.22 ± 2.20	10.34 ± 0.37	366	643
High Females (8)	39.83 ± 5.63	11.96 ± 0.65	324	562
Low Females (13)	32.48 ± 3.75	10.02 ± 0.32	329	556

Trial 8

The foregoing study indicated that when birds are administered thiouracil, the individuals retaining the greatest resistance to fatigue generally had the largest thyroid glands. Because of this observation, it was reasoned that under similar conditions of thiouracil administration, the high-thiouracil-response strain of birds used in trial 3 should possess a higher exhaustion period than the low-response strain. Therefore, the following study was conducted in an attempt to determine the validity of this postulation: Two groups of birds 31 days of age were chosen, each group containing 8 males and 8 females. One group consisted of individuals from the low-response strain, while the second consisted of individuals from the high-response strain. Prior to being placed on a diet containing 0.2 per cent thiouracil, the exhaustion revolutions of both groups were determined twice at 12 r.p.m. At the end of 1 and 2 weeks the revolutions required to exhaust both groups was again determined twice at 12 r.p.m. When the study was terminated, 3 weeks after placing the birds on thiouracil, the 2 groups were autopsied.

As shown in Table XII, there was no great difference between the two groups with respect to the revolutions required to exhaust them; particularly when one considers the large individual variation. It was indicated by the mean and median exhaustion revolutions that the low-response group was more resistant to fatigue than the high- during the first 5 times they were revolved. Yet on the sixth revolving (after a little over 2 weeks on thiouracil), the high-response group

seemed to be more resistant. The most resistant individual was from the high-response group and this bird also had the largest thyroid weight observed in this trial (97.59 mg./100 gm. of body weight).

With the exception of the thyroids, which were larger in the high-response group, there was little difference between the two groups with respect to the other gland weights (Table XIII). However, all the glands considered were slightly larger in the high-response group.

TABLE XII

THE REVOLUTIONS REQUIRED TO EXHAUST THE HIGH- AND LOW-THIOURACIL-RESPONSE BIRDS AFTER 1 AND 2 WEEKS ON 0.2% THIOURACIL

(Trial 8)

GROUP	Number of Weeks on 0.2% Thiouracil					
	0		1		2	
	12 r.p.m.		12 r.p.m.		12 r.p.m.	
High Response						
Mean	71	278	132	382	360	811
Median	45	180	119	215	138	181
Range	28-136	29-816	15-240	30-1324	50-1476	25-8100
Low Response						
Mean	180	749	282	806	497	672
Median	93	310	113	265	226	154
Range	42-660	40-2688	23-1960	58-5882	52-444	43-5064

TABLE XIII

THE AVERAGE WEIGHTS OF THE GLANDS DESIGNATED FOR THE HIGH- AND LOW-THIOURACIL-RESPONSE BIRDS FOLLOWING 3 WEEKS ON 0.2% THIOURACIL

(Trial 9)

GROUP	Weight in mg./100 gm. of body wt.					Body Wt.Gm.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Init.	Fin.
High Response							
Males (8)	1.05±0.06	55.07±8.63	12.30±0.61	256.3±24.3	162.1±15.0	333	691
Females (8)	1.05±0.10	57.94±7.87	11.66±0.66	256.0±15.2	203.7±14.3	280	548
Low Response							
Males (7)	0.88±0.08	19.48±2.15	11.46±1.10	213.1±17.3	154.1±13.8	381	839
Females (8)	0.89±0.07	25.32±2.76	11.36±1.10	241.6±29.3	197.3±21.0	343	709

Trial 9

This trial consisted of several studies planned in an effort to increase the exhaustion revolutions of chickens. With this thought in mind, studies using cortisone injections, testosterone implantation, and protamone administration were conducted. Because of the great variation in the number of revolutions required to exhaust randomly selected chickens, it was deemed necessary to first determine the resistance of the chickens to muscular fatigue. Therefore, for a given study, a large number of New Hampshires (between 100 and 125) were selected and these were revolved twice at 12 r.p.m. Only those birds requiring fewer than 48 revolutions to exhaust during the second revolving were used in the studies. After these birds had been obtained, they were divided into control and experimental groups. Treatment of the experimental birds was begun two days prior to the time that the groups were exercised again. The paragraph discussing each study is appropriately designated as cortisone study, etc.

Cortisone Study: Prior to commencing this study, an investigation was conducted for the purpose of ascertaining the toxicity of cortisone for young chickens. For this purpose, 6 comparable groups of 5 birds one-week of age were selected. For a period of 10 days, groups 1, 2, 3, 4, and 5 received daily injections of cortisone at levels of 1, 5, 10, 20, and 50 mg./kg. of body weight respectively. A sixth group constituted the control. The percentage reduction in growth rate was considered as being indicative of the degree of toxicity. In figure 8, it is indicated that daily injections exceeding 5 mg./kg. of body weight were toxic. After obtaining the foregoing information, two

trials were conducted using cortisone. In the first, daily cortisone injections of 5.0 mg./kg. of body weight were used. Since this dosage level seemed too high, a second trial was made using daily injections of 2.5 mg./kg. of body weight. In the 2 trials, 12 birds 32 days of age were used in both the control and experimental groups. The groups were comparable with respect to weight, resistance to muscular fatigue, and sex. The experimental groups received injections daily for 9 days in the pectoral muscles. All control birds received injections of saline quanitatively equal to the cortisone administered. Both groups of each trial were revolved twice at 12, 17, and 22 r.p.m. The birds in the first trial were exercised an additional time at 17 r.p.m. At the end of each study, both groups were autopsied.

Cortisone injections at levels of 2.5 and 5.0 mg./kg. of body weight were found not to augment the resistance of these birds to fatigue (Table XIV). Actually a reduction in resistance occurred following cortisone injections. No explanation can be given for the exceptional individual (see Table XIV) in the group injected with 5.0 mg. of cortisone. Since the subsequent resistance of this animal to fatigue was so much greater than noted for the other individuals of this group, it was not included when the mean and median exhaustion values were computed.

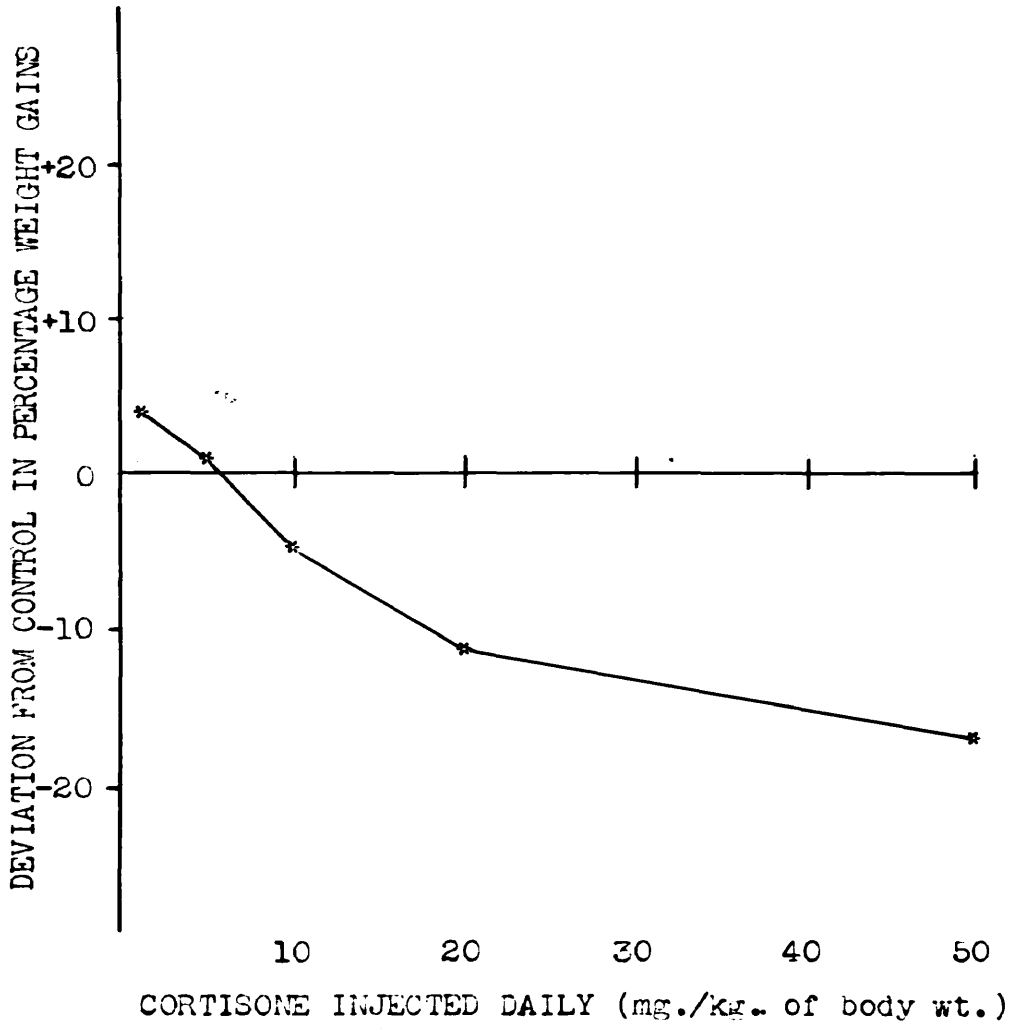

Figure 8. The effect of 10 daily injections of cortisone at the levels indicated on the percentage weight gains of young New Hampshires.

TABLE XIV

THE REVOLUTIONS REQUIRED TO EXHAUST THE CONTROL AND EXPERIMENTAL BIRDS OF THE CORTISONE STUDY AT THE R.P.M. INDICATED

(Trial 9)

5.0 mg. of Cortisone/kg. of Body Weight

GROUP:

	Revolutions Per Minute						
	12	12	17	17	22	22	22
Control:							
Mean	224	353	240	248	565	284	367
Median	92	217	150	221	350	275	354
Range	22-1025	55-1020	88-748	48-849	27-1020	81-629	66-781
Experimental:							
Mean	132	113	126	138	190	136	128
Median	90	124	84	82	139	139	121
Range	49- 234	19- 552	36-296	31-532	37- 745	26-244	40-293
Exceptional Individual	1266	1513	209	4721	3091	1078	3133

2.5 mg. of Cortisone/kg. of Body Weight

	Revolutions Per Minute					
	12	12	17	17	22	22
Control:						
Mean	110	314	238	247	117	158
Median	59	56	162	189	95	139
Range	17- 735	23-1387	19-553	27-646	37- 286	31-339
Experimental:						
Mean	102	180	94	99	75	86
Median	36	74	80	54	64	70
Range	10- 637	12- 777	14-437	20-536	22- 139	31-176

There was little difference between the control and experimental groups with respect to the weights for the various glands as shown in Table XV. The pituitaries of the experimental birds were larger, particularly for the group injected daily with 5.0 mg. of cortisone/kg. of body weight. There was reduction in the weight of the bursae and spleens of this group below that for the control, but not for the group receiving 2.5 mg. of cortisone daily.

There was an indication as shown by the final body weights that the growth rate of the experimental birds had been adversely affected. It was found that an occasional bird injected with cortisone underwent a mild convulsion at the time of the injection. In a matter of minutes, these individuals seemed to recover.

Protamone Study: This study was conducted for the purpose of observing the effect of protamone administration on the birds displaying low resistance to fatigue. Two comparable groups of 12 low-exhaustion birds 32 days of age were selected; one constituted the control and the second was given 0.03 per cent of protamone in their feed. Over a period of 6 days, the birds of both groups were exercised to exhaustion twice at 12, 17, and 22 r.p.m. When the study was terminated, all the birds were autopsied.

The mean and median revolutions required to exhaust the birds at each r.p.m. are given in Table XVI. These results have also been plotted in figure 9. There is a definite indication that protamone has increased the resistance of the experimental group to fatigue.

TABLE XV

THE AVERAGE GLAND WEIGHTS FOR THE CONTROL AND EXPERIMENTAL BIRDS OF THE CORTISONE STUDY

(Trial 9)

5.0 mg. of Cortisone/kg. of Body Weight

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Init.	Final
Control							
Males (4)	1.04 ± 0.09	7.30 ± 0.35	12.57 ± 0.69	433.1 ± 73.6	233.5 ± 35.9	375	528
Females (8)	1.10 ± 0.05	7.71 ± 0.77	12.71 ± 0.56	406.9 ± 42.2	232.8 ± 16.6	319	445
Experimental							
Males (4)	1.34 ± 0.07	7.89 ± 1.04	15.05 ± 0.82	354.1 ± 43.1	198.1 ± 18.1	348	438
Females (8)	1.13 ± 0.05	8.22 ± 0.45	12.67 ± 0.67	366.7 ± 39.1	196.9 ± 13.3	328	438

2.5 mg. of Cortisone/kg. of Body Weight

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Init.	Final
Control							
Males (8)	0.91 ± 0.05	6.95 ± 0.34	11.54 ± 0.86	448.3 ± 37.8	189.4 ± 7.9	340	566
Females (4)	0.91 ± 0.07	8.60 ± 0.54	11.86 ± 1.40	317.5 ± 21.0	245.0 ± 14.3	319	510
Experimental							
Males (7)	0.96 ± 0.06	6.35 ± 0.68	12.00 ± 0.71	428.0 ± 30.7	212.9 ± 15.2	338	569
Females (5)	1.08 ± 0.04	8.48 ± 0.82	10.91 ± 0.84	359.0 ± 37.1	259.1 ± 14.8	306	489

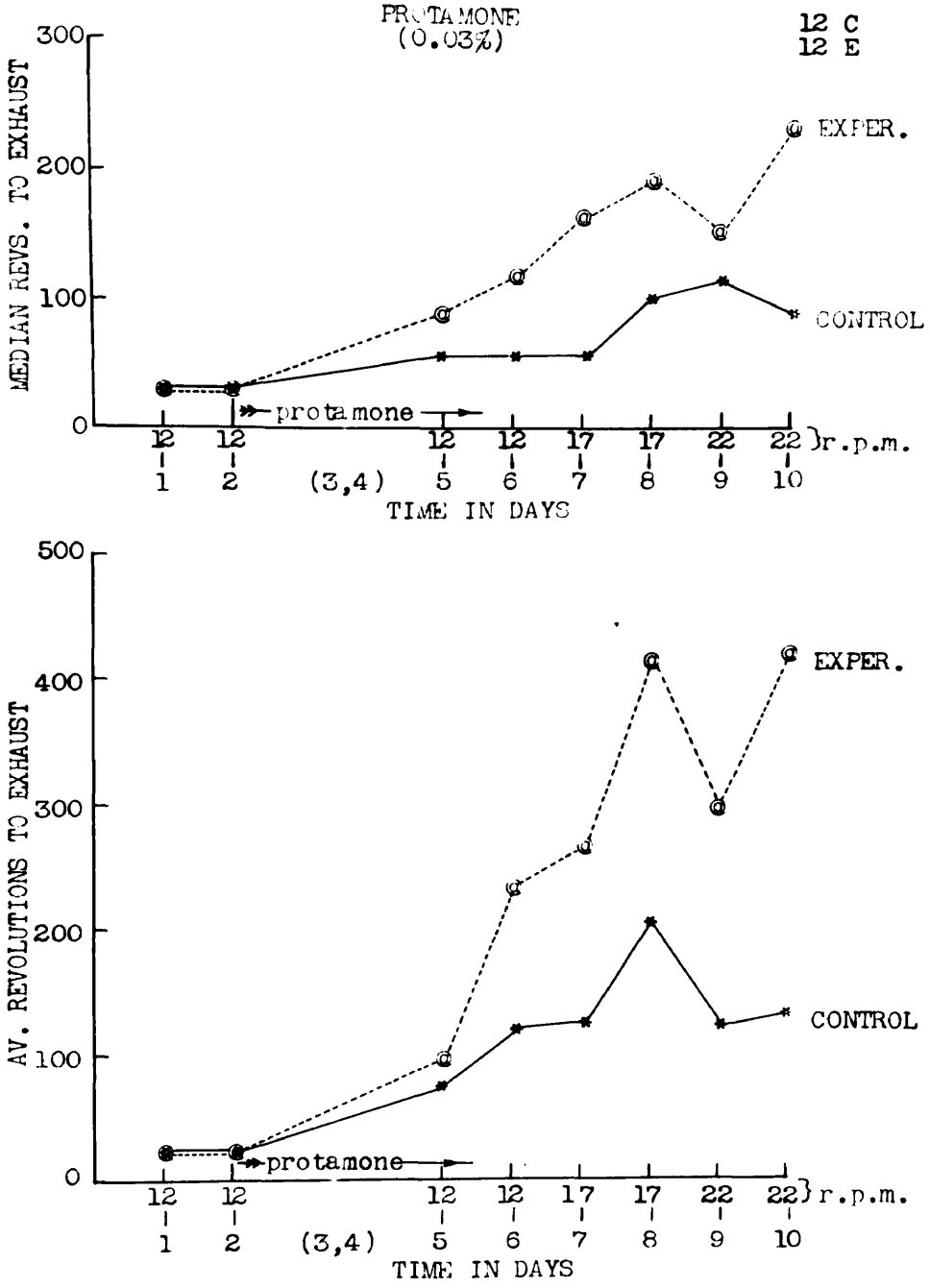

Figure 9. The effect of protamone on the exhaustion revolutions of birds showing low resistance to fatigue.

TABLE XVI

THE REVOLUTIONS REQUIRED TO EXHAUST THE CONTROL AND EXPERIMENTAL BIRDS OF THE PROTAMONE STUDY AT THE R.P.M. INDICATED

(Trial 9)

	Revolutions Per Minute					
GROUP	12	12	17	17	22	22
Control:						
Mean	69	116	121	204	116	128
Median	52	55	51	99	114	88
Range	20-192	18-510	31-517	26- 872	33-323	40- 330
Experimental:						
Mean	94	232	267	412	295	422
Median	88	119	169	191	151	236
Range	38-252	24-606	60-643	119-1620	55-865	103-1441

TABLE XVII

THE AVERAGE GLAND WEIGHTS FOR THE CONTROL AND EXPERIMENTAL BIRDS OF THE PROTAMONE STUDY

(Trial 9)

	Weight in mg./100 gm. of Body Wt.					Body Wt. Gms
GROUP	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Init. Fin.
Control:						
Males (6)	0.93±0.07	6.90±1.23	13.59±1.15	383.5±38.9	212.0±19.1	384 519
Females (5)	0.78±0.06	9.53±0.74	10.87±0.42	485.0±34.5	235.4±24.0	405 554
Experimental:						
Males (6)	0.79±0.05	4.19±0.32	11.61±0.48	466.0±51.3	169.4±15.1	437 571
Females (5)	0.85±0.05	5.17±0.39	11.18±0.42	494.0±31.0	233.9±15.2	389 494

With the exception of the thyroids, the gland weights for the control and experimental groups differed only slightly as shown in Table XVII. The thyroids, of course, were smaller for the birds given protamone. It was noted that the bursae of the experimental birds were larger, especially those for the males.

Testosterone Study: It has been noted in a number of the previous trials that the males seemed to be more resistant to fatigue than the females. This same phenomenon was encountered when searching for the low resistant individuals used in the present series of studies. The larger number of the resistant individuals were found to be males. Therefore, the present study was designed to ascertain whether or not the male sex hormone affected the resistance of the low-exhaustion birds. For this investigation, two comparable groups of 12 birds 34 days of age were obtained in the same manner as the previous groups. One of these was designated as control while the individuals of the second group were implanted in the neck region with a 4.4 mg. pellet of testosterone. Over a period of one week, both groups were exercised until exhausted for 2 times at 12 r.p.m., 2 times at 17 r.p.m. and 3 times at 22 r.p.m., after which they were autopsied.

The results of this study are shown in Table XVIII and figure 10. There seemed to be no difference between the two groups with regard to their resistance to fatigue until they were revolved for the second and third time at 22 r.p.m. At that time, the resistance of the group implanted with testosterone was greater. The combs of the experimental birds showed a marked increase in size during the last days of this study.

There was no great difference between the gland weights of the two groups, (Table XIX). It might be mentioned that the bursae of the birds implanted with testosterone were smaller.

TABLE XVIII

THE REVOLUTIONS REQUIRED TO EXHAUST THE CONTROL AND EXPERIMENTAL BIRDS OF THE TESTOSTERONE STUDY AT THE R.P.M. INDICATED

(Trial 9)

	Revolutions Per Minute						
GROUP	12	12	17	17	22	22	22
Control:							
Mean	50	137	65	125	244	104	86
Median	44	71	46	79	85	88	63
Range	12-114	18-726	22-145	12-408	42-1980	44- 282	24- 264
Experimental:							
Mean	74	117	157	222	148	293	617
Median	41	73	112	73	112	172	227
Range	12-324	20-397	54-502	31-991	42- 440	55-1767	51-2004

TABLE XIX

THE AVERAGE GLAND WEIGHTS OF THE CONTROL AND EXPERIMENTAL BIRDS OF THE TESTOSTERONE STUDY

(Trial 9)

	Weight in mg./100 gm. of Body Wt.				Body Wt.Gms	
GROUP	Pitui.	Adrenal	Bursa	Spleen	Init.	Fin.
Control:						
Males (5)	1.02 ± 0.15	11.35 ± 1.28	444.6 ± 32.5	217.4 ± 31.6	432	544
Females (7)	0.92 ± 0.05	9.31 ± 0.71	494.9 ± 19.1	230.7 ± 21.1	369	485
Experimental:						
Males (4)	0.98 ± 0.09	11.45 ± 0.25	363.3 ± 37.7	169.3 ± 3.3	384	517
Females (7)	0.97 ± 0.08	9.83 ± 0.55	445.2 ± 34.5	247.7 ± 20.4	389	508

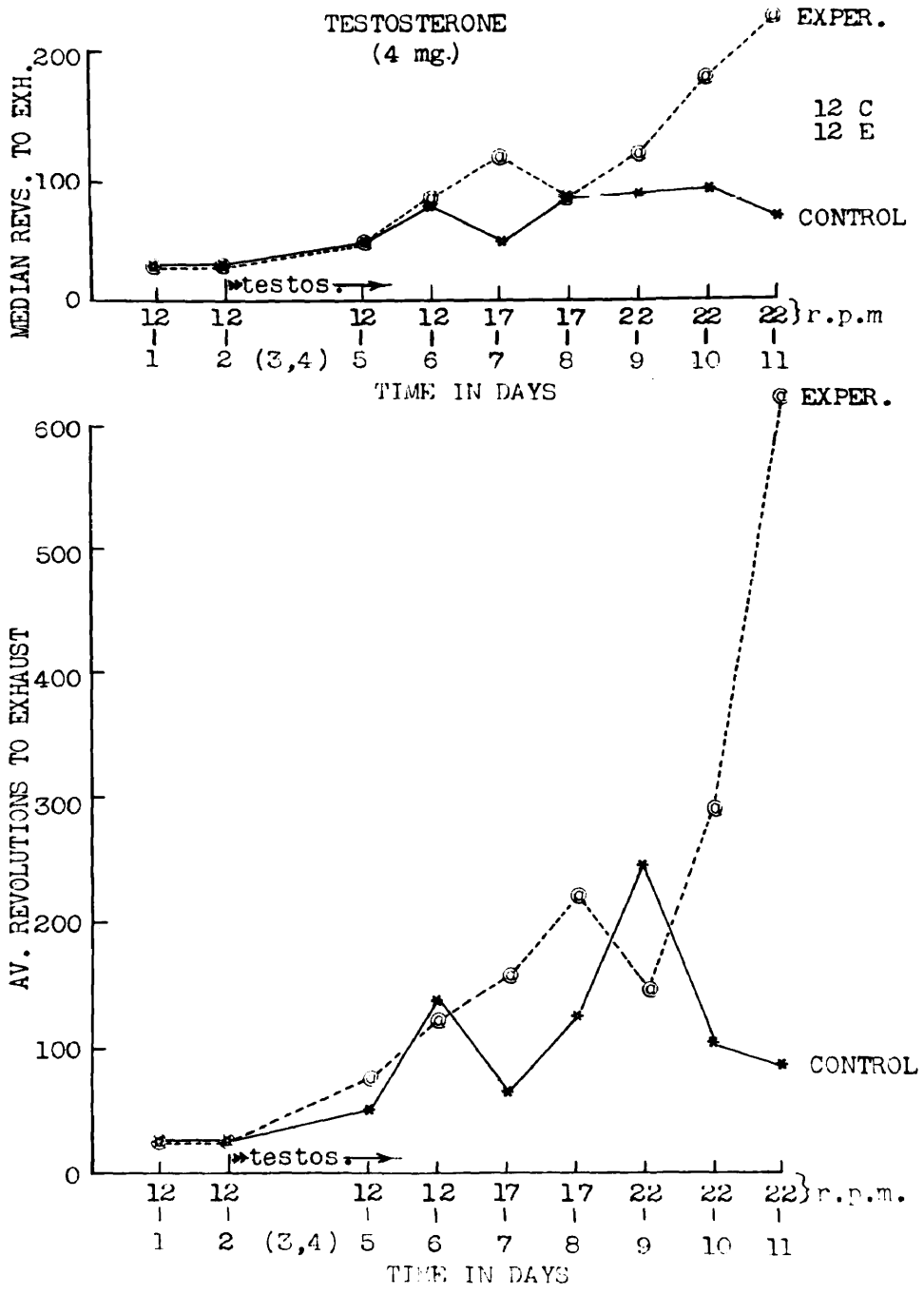

Figure 10. The effect of testosterone on the exhaustion revolutions of birds showing low resistance to fatigue.

PHASE II

Cold Response Study

Trial 10

Preliminary investigations had suggested that certain morphological changes occurring in various glands upon exposure of New Hampshires to cold varied with the length of exposure. Therefore, this trial was conducted which consisted of four different studies designed to investigate the stress response of New Hampshires 47 to 49 days old to conditions of cold. An ambient temperature of 40° to 44° F. was maintained for all four exposure periods of 1, 2, 3, and 4 weeks. Both the control and experimental group for a given study contained 13 females and 11 males. The effects of these exposure periods on the weight of the pituitary, thyroids, adrenals, bursa, and spleen were investigated. In addition, the body weight of the birds was considered.

The results of this study are presented in Table XX. It is seen that for the four control groups, the males had slightly smaller thyroids and spleens and generally had larger adrenals and bursae. These differences, while not pronounced, were found to be consistent with subsequent observations.

Following 1, 2, 3, and 4 weeks exposure to cold, it was noted that the adrenals of the males were heavier than for the females. The bursae, spleens, and thyroids were smaller for the males following all periods of exposure. (i.e., smaller than for the females of

the experimental groups).

In figure 11 is presented the percentage which the various glands were noted to deviate in weight from the control. For the preparation of this figure, both the males and females were considered together. It is seen that the adrenals of the experimental groups are larger than for the control after all periods of exposure. The same is true for the pituitary except at 4 weeks, where there seemed to be no difference between the control and experimental groups. It is seen that the bursae and spleens of the experimental birds are smaller for all periods. Of interest is the observation that the thyroids decrease in weight at one week, return to control weight at 2, increase at 3, and decrease in weight again at 4 weeks.

The body weight of the experimental birds was below that for the control following all exposure periods.

TABLE XX

THE EFFECT OF 1, 2, 3, AND 4 WEEKS EXPOSURE OF NEW HAMPSHIRES TO COLD (40 to 44° F.) ON THE WEIGHTS OF THE GLANDS INDICATED

(Trial 10)

	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
Cold For One Week							
Control:							
Males (11)	0.82 ± 0.09	9.18 ± 0.85	10.37 ± 0.52	519.7 ± 32.1	230.0 ± 13.1	782	973
Females (13)	0.70 ± 0.04	11.03 ± 0.53	10.11 ± 0.33	429.0 ± 29.2	259.4 ± 20.5	674	826
Experimental:							
Males (11)	0.88 ± 0.06	8.12 ± 0.66	12.55 ± 0.78	388.2 ± 35.1	193.1 ± 13.6	788	882
Females (12)	0.72 ± 0.03	8.49 ± 0.53	10.76 ± 0.41	447.6 ± 40.0	235.9 ± 11.1	672	779
Cold For Two Weeks							
Control:							
Males (11)	0.75 ± 0.05	8.53 ± 0.41	9.12 ± 0.44	471.6 ± 42.4	222.1 ± 10.6	673	1079
Females (13)	0.63 ± 0.03	10.31 ± 0.58	8.68 ± 0.33	379.8 ± 23.5	246.0 ± 13.8	597	904
Experimental:							
Males (11)	0.82 ± 0.04	8.55 ± 0.79	11.79 ± 0.80	373.0 ± 27.4	209.4 ± 7.8	678	1020
Females (12)	0.72 ± 0.04	10.38 ± 0.54	10.53 ± 0.34	383.2 ± 21.2	241.5 ± 14.1	597	869
Cold For Three Weeks	(Cont'd. on next page)						

TABLE XX, Cont'd.

THE EFFECT OF 1, 2, 3, AND 4 WEEKS EXPOSURE OF NEW HAMPSHIRES TO COLD (40 to 44°F.) ON THE WEIGHTS OF THE GLANDS INDICATED

(Trial 10)

	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
Control:							
Males (11)	0.57± 0.03	8.51± 0.63	9.16± 0.48	341.9± 25.9	277.1± 29.0	808	1425
Females (13)	0.61± 0.02	8.96± 0.38	8.93± 0.40	384.7± 27.4	288.0± 16.1	746	1202
Experimental:							
Males (11)	0.78± 0.05	9.26± 0.90	11.86± 0.88	338.4± 28.3	250.0± 47.9	806	1263
Females (13)	0.71± 0.04	11.89± 0.83	11.19± 0.34	367.2± 31.2	272.8± 18.4	752	1178
Cold For Four Weeks							
Control:							
Males (11)	0.67± 0.04	9.75± 0.77	9.22± 0.29	458.8± 52.9	279.3± 40.1	714	1428
Females (11)	0.60± 0.04	11.52± 0.62	8.54± 0.27	391.1± 30.8	294.1± 36.9	648	1203
Experimental:							
Males (11)	0.62± 0.04	8.03± 0.75	10.23± 0.76	356.4± 24.9	207.8± 9.9	703	1308
Females (12)	0.65± 0.04	9.93± 0.90	9.85± 0.41	418.6± 34.9	245.2± 27.2	649	1140

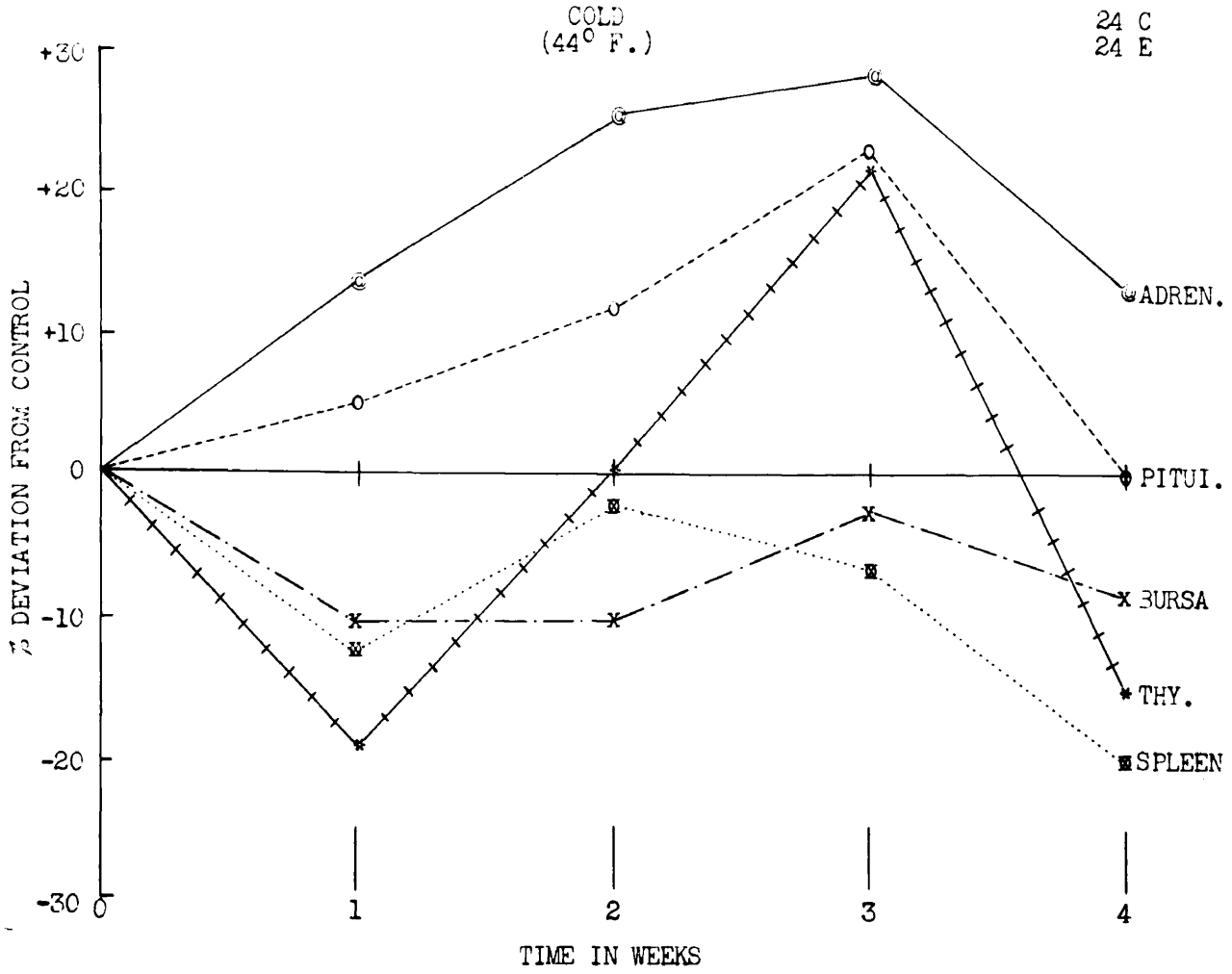

Figure 11. The percentage which the designated gland weights of New Hampshires were noted to deviate from the control groups after 1, 2, 3, and 4 weeks exposure to cold (40 to 44° F.).

Trial 11

This study was conducted for the purpose of determining whether there was a pronounced difference in the reaction of the high- and low-thiouracil-response strains to conditions of cold. Four groups of birds were chosen, each of which contained 5 males and 7 females 40 days of age. Two of the groups were selected from the low-response strain and 2 from the high-response strain. One group of each strain was placed in a cold room for 2 weeks at 40° to 44° F. The remaining 2 groups constituted the control.

It is indicated in Table XXI that the pituitaries and thyroids of the high-response control group weighed slightly more than these glands for the low-response controls. However, it is reasonably certain that the differences observed are not statistically significant. The other glands considered for the control group of each strain were comparable in weight. Cold seemed to cause a slight increase in adrenal weight, which was similar for both strains. The bursae and spleens of the experimental group of birds also regressed in weight except for the males of the low-response strain where an increase was suggested.

TABLE XXI

THE EFFECT OF COLD ON THE DESIGNATED GLAND WEIGHTS OF BIRDS FROM THE HIGH- AND LOW-THIOURACIL RESPONSE STRAINS

(Trial 11)

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pitui.	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
High Response							
Control:							
Males (5)	0.88 ± 0.10	8.77 ± 0.73	11.04 ± 0.46	433.2 ± 43.9	199.8 ± 17.0	571	878
Females (7)	0.84 ± 0.06	8.88 ± 1.04	11.09 ± 0.40	423.7 ± 28.5	207.2 ± 16.1	473	714
Experimental:							
Males (5)	0.80 ± 0.06	7.75 ± 1.00	13.12 ± 0.83	371.2 ± 50.1	220.7 ± 27.1	555	854
Females (6)	0.95 ± 0.03	11.27 ± 1.51	13.61 ± 0.54	327.3 ± 52.9	237.2 ± 21.0	461	717
Low Response							
Control:							
Males (5)	0.82 ± 0.06	7.42 ± 1.10	10.77 ± 1.14	424.6 ± 60.3	188.1 ± 17.2	479	722
Females (7)	0.67 ± 0.05	7.49 ± 0.90	10.46 ± 1.02	352.3 ± 45.5	228.5 ± 26.0	453	701
Experimental:							
Males (5)	0.93 ± 0.07	7.23 ± 0.57	13.20 ± 0.96	490.2 ± 37.3	286.4 ± 46.3	475	747
Females (6)	0.81 ± 0.09	8.47 ± 0.89	11.94 ± 0.59	258.7 ± 27.2	236.6 ± 29.3	464	676

PHASE III

EFFECT OF SHORT PERIODS OF STRESS

Trial 12

This phase of the investigation was undertaken to determine how soon after exposure of the birds to various forms of stress is it possible to recognize changes in the organ and gland weights. In the present trial four comparable groups of New Hampshires 21 days of age were selected and these were designated A, B, C, and D. Each group was subjected to the following conditions: A - Control. B - Each bird of this group was revolved for 60 minutes every third hour at 4 r.p.m. during a period of 24 hours (total of 8 hours per bird). C - Each bird was exposed to simulated altitudes of 12 to 15,000 feet for 2 hours of every 4 during a 24 hour period (12 hours total per bird). D - These birds were placed in a cold room at 32° F. for the 24 hour period. Neither the control nor experimental groups were given feed or water during the study.

Before presenting the results obtained for the weights of the various glands, it would probably be well to mention a few observations made in the course of this study. While 4 r.p.m. was a very slow speed, occasionally an individual became completely exhausted and was unable to continue walking in the cages. However, these birds were not removed from the cages until the end of the hour when they were usually in an unconscious state. A few minutes after they were taken from the revolving cages, they seemed to recover almost

completely. It was interesting to note in this study and also in a preliminary study associated with it, that the birds unable to complete the hour's walk were usually the poorest feathered individuals. While the scope of this trial was not broad enough to confirm this observation, it might prove interesting to investigate it further. These birds, the youngest used thus far, seemed to have larger relative pituitary weights than the older birds used previously. A comparison of the weights for this gland given in Table XXII with those given in previous Tables will illustrate this observed difference.

As shown in Table XXII, all three stress stimuli apparently caused an increase in the weights of the adrenals. This increase in the weights of the adrenals seemed to be most pronounced for the males which were exposed to muscular exercise and high altitudes. Attention is directed to the large standard error for the adrenal weights of the birds subjected to cold. It was found that some individuals of this group responded with a profound increase in adrenal weight while no apparent effect was exerted on the glands of other individuals. The four largest adrenal weights observed in this trial were glands which had been dissected from birds of this group.

The bursae and spleens of the birds exposed to muscular exercise were smaller, particularly those for the females. It was noted that the bursae of birds placed at high altitudes were also smaller. There was an indication that the spleens from the females of this group were smaller.

While the bursae of the birds kept in cold weighed less than the bursae of the control birds, the difference was quite small. The

spleens of these birds seemed to be slightly larger.

There were no pronounced differences in the weights of the pituitary glands for the four groups. However, with one exception, this gland weight was less for the birds of each sex which had been under condition of stress. The only exceptional group were the females which had been subjected to cold. The thyroid weights for the four groups were similar.

All four groups showed a reduction in body weight during the 24 hour period which was most pronounced for the experimental groups.

TABLE XXII

THE GLAND WEIGHTS OF CHICKENS EXPOSED TO THE DESIGNATED CONDITIONS OF STRESS

(Trial 12)

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pituitary	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
A. Control:							
Males (5)	1.87 ± 0.14	9.53 ± 0.77	19.85 ± 1.09	476.2 ± 59.3	164.2 ± 17.1	223	202
Females (7)	1.70 ± 0.13	8.75 ± 0.81	17.85 ± 1.34	437.1 ± 33.7	181.3 ± 14.6	188	170
B. Exercise:							
Males (5)	1.76 ± 0.11	8.69 ± 0.96	26.57 ± 1.42	320.1 ± 18.7	146.8 ± 15.0	213	175
Females (7)	1.60 ± 0.13	10.30 ± 0.61	20.76 ± 0.58	353.5 ± 12.7	122.9 ± 12.4	202	172
C. Altitude:							
Males (5)	1.77 ± 0.24	9.22 0.98	27.62 0.77	333.6 18.2	164.0 33.0	199	168
Females (7)	1.45 ± 0.09	10.52 0.74	22.79 1.13	352.4 28.3	143.1 18.5	204	175
D. Cold:							
Males (5)	1.61 ± 0.09	9.41 ± 1.06	22.71 ± 3.17	419.8 ± 59.6	239.8 ± 21.6	222	191
Females (7)	1.70 ± 0.14	8.09 ± 0.68	24.63 ± 2.39	422.3 ± 35.0	232.6 ± 16.2	193	166

Trial 13

This trial was conducted in order to observe the effects of emotional stress on the various gland weights. Two comparable groups of New Hampshires were selected with 12 birds 29 days of age in each group (6 males and 6 females). The birds of the experimental group were carefully bound by the feet and wings with rubber bands 3/8 inches wide and by means of hooks, the bands were fastened to hardware cloth (refer to figure 4). These birds were left in this position for 24 hours. Neither the control nor the experimental group was fed or watered during that period. Following this exposure period, both groups were autopsied. Actually this experiment was conducted as a preliminary study in conjunction with the trial to follow. It was one of a series of attempts designed to discover a stress stimuli mild enough not to cause death over extended periods of time and yet severe enough to elicit a discernible response within a few hours. However, since it was found that simulated altitudes of 12,000 to 15,000 feet more nearly met the requirement for this form of stress, the emotional aspect, as such, was not considered beyond this trial. But as a matter of interest, the results of this study are being reported.

During the 24 hour period, the experimental birds struggled very little. It should be mentioned that for about 1/2 of the birds, the rubber bands impaired circulation in the extremities.

In Table XXIII, are given the gland weights obtained for the birds in this study. While the differences are probably not statistically significant, it is seen that the pituitaries, thyroids, bursae,

and spleens of the experimental group were smaller. The adrenals were somewhat larger for the experimental group. It was noted that individuals suffering from impaired circulation possessed the smallest spleens.

TABLE XXIII

THE EFFECT OF FORCED IMMOBILIZATION ON THE GLAND WEIGHTS OF NEW HAMPSHIRES

(Trial 13)

GROUP	Weight in mg./100 gm. of Body Wt.				
	Pitui.	Thyroid	Adrenal	Bursa	Spleen
Control: (6M., 6F.)	1.14±0.07	6.76±0.69	13.43±0.80	463.7±32.4	170.4±20.4
Experimental: (6M., 6F.)	0.93±0.05	6.17±0.35	15.26±0.68	352.3±32.5	116.4±19.2

	Body Weight, Grams	
	Initial	Final
Control: (6M., 6F.)	353	312
Experimental: (6M., 6F.)	353	317

Trial 14

This investigation was designed to consider the effect of even shorter periods of stress than used in previous trials. The experimental birds in each of five trials were exposed to simulated altitudes of 12,000 to 15,000 feet for periods of 1, 2, 3, 4, and 5 hours. Both the experimental and control groups for each exposure period contained 2 New Hampshires (10 males and 10 females) 21 to 22 days of age, except the 2-hour study which contained 50 birds (26 males and 24 females in each group). Neither the control nor the experimental groups were fed or watered during these studies. The initial body weights were used in computing gland weights/100 gm. of body weight.

The results of this trial are given in Table XXIV. As observed previously in trial 12, the relative pituitary weights for birds of this age were greater than has been noted for the somewhat older birds used in other studies. The control and experimental males of each exposure period consistently had larger adrenals than the females of their group. Generally the bursae and spleens of the control males were smaller than for the control females, but not remarkably so. Similarly, the spleens of the experimental males were usually smaller, except after 5 hours of exposure when the reverse situation was indicated. With the exception of the 1 and 2 hour exposure periods, the bursae of the experimental males weighed slightly more than for the experimental females.

In figure 12 is plotted the percentage which the various glands of the experimental birds (males and females combined) deviated in

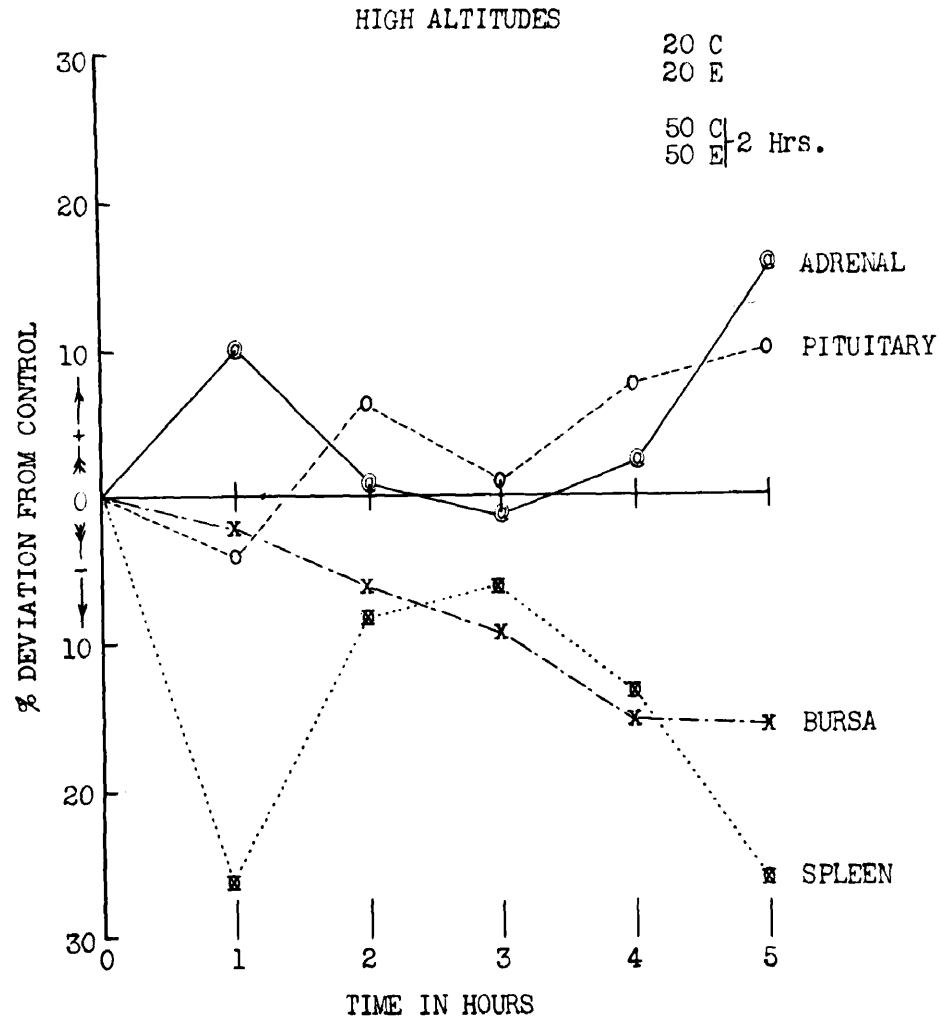

Figure 12. The percentage which the glands of New Hampshires deviated in weight from the control groups following 1, 2, 3, 4, and 5 hours at simulated altitudes of 12 to 15,000 feet.

weight from the control birds following each exposure period. It is seen that a slight increase in adrenal weight seems to occur following one hour of exposure, with an increase in weight not becoming apparent again until after 5 hours at this condition. It is noted that the pituitary of the experimental birds is slightly heavier after 2, 3, 4, and 5 hours of exposure. The bursae and spleens became progressively lighter as the study continued; a pronounced drop in spleen weight occurring after one hour of exposure.

TABLE XXIV

THE EFFECT OF SIMULATED ALTITUDES OF 12-15,000 FEET FOR PERIODS OF 1, 2, 3, 4, AND 5 HOURS ON THE AVERAGE GLAND WEIGHTS OF NEW HAMPSHIRES

(Trial 14)

GROUP	Weight in mg./100 gm. Body Wt.				Body Wt.
	Pituitary	Adrenal	Bursa	Spleen	Grams
One Hour					
Control:					
Male (10)	1.27±0.08	13.27±0.68	395.7±36.8	219.9±15.6	251
Female (10)	1.30±0.08	12.47±0.47	449.5±35.4	253.7±10.1	224
Experimental:					
Male (10)	1.24±0.10	14.29±0.79	384.2±29.3	146.2± 9.1	250
Female (10)	1.23±0.07	13.99±0.65	446.1±48.6	204.4±16.0	224
Two Hours					
Control:					
Male (26)	1.41±0.07	15.43±0.57	441.5±21.5	177.0± 9.6	200
Female (24)	1.31±0.06	13.37±0.44	475.2±25.3	201.6±17.1	194
Experimental:					
Male (24)	1.49±0.06	15.25±0.55	386.9±25.1	168.5±14.9	202
Female (26)	1.41±0.06	14.02±0.38	461.8±14.0	186.2± 9.9	190
Three Hours					
Control:					
Male (10)	1.36±0.13	15.35±0.88	430.4±55.1	172.5±20.0	243
Female (10)	1.43±0.11	13.40±0.88	434.1±31.0	186.3±15.7	207
Experimental:					
Male (10)	1.42±0.08	14.26±0.72	417.9±36.0	152.0±16.1	238
Female (10)	1.34±0.05	14.20±0.63	362.5±44.3	190.0±20.0	208
Four Hours					
Control:					
Male (10)	1.29±0.09	14.20±0.65	481.6±26.8	189.2±13.7	237
Female (10)	1.36±0.07	13.80±0.84	464.1±38.4	214.6±17.1	202
Experimental:					
Male (10)	1.40±0.17	15.06±0.52	400.1±41.5	159.7±13.8	239
Female (10)	1.33±0.07	13.55±0.52	402.5±19.5	191.3±16.7	201

(Continued on next page)

TABLE XXIV, (Continued)

THE EFFECT OF SIMULATED ALTITUDES OF 12-15,000 FEET FOR PERIODS OF 1, 2, 3, 4, AND 5 HOURS ON THE AVERAGE GLAND WEIGHTS OF NEW HAMPSHIRES

(Trial 14)

GROUP	Weight in mg./100 gm. Body Wt.				Body Wt.
	Pituitary	Adrenal	Bursa	Spleen	Grams
Five Hours					
Control:					
Male (10)	1.26±0.06	14.76±0.66	484.4±31.5	183.4±15.7	216
Females (10)	1.23±0.10	13.12±0.48	444.7±33.1	175.8±15.5	195
Experimental:					
Male (10)	1.45±0.08	17.04±0.62	374.7±22.2	150.7±21.5	239
Female (10)	1.29±0.11	15.32±0.64	411.6±25.7	132.6± 9.8	201

PHASE IV

Thiouracil and Protamone Study

Trial 15

It was noted in certain of the foregoing trials (trials 6 and 7) that the adrenal weights of the birds fed thiouracil for two weeks were either comparable with or less than those of the control. In addition, the bursae and spleens of these birds were consistently smaller. But in a preliminary study, there was evidence to indicate that the adrenals of birds administered thiouracil became enlarged a short time after placing young chickens on such a diet. This preliminary study consisted of two comparable groups of 9 New Hampshires, one group of which was administered thiouracil for 3-1/2 days. At the end of this period, both the experimental and control groups were autopsied. It is noted in Table XXV that the adrenals of the experimental birds were greatly enlarged, while the bursae were smaller. Because of these conflicting observations with respect to adrenal weights after thiouracil feeding, a series of studies were undertaken to determine the effect of 3, 6, 9, and 12 day periods of thiouracil administration on the various glands. At the same time, the effect of feeding protamone to similar groups for these periods of time was also investigated. To accomplish this end, 12 similar groups of New Hampshires 31 days of age were selected. Each group contained 10 males and 10 females. For a given experimental period of 3, 6, 9, and 12 days, 3 groups were used. One group constituted the control while a

TABLE XXV

THE EFFECT OF THIOURACIL (0.02%) FOR 3-1/2 DAYS ON THE AVERAGE GLAND WEIGHTS OF NEW HAMPSHIRES

(Trial 15)

GROUP	Weight in mg./100 gm. Body Wt.				Body Wt., Gms	
	Pituitary	Thyroid	Adrenal	Bursa	Init.	Final
Control:						
(5M., 4F.)	1.47±0.08	7.39±0.38	17.55±0.85	398.9±29.4	212	234
Experimental:						
(5M., 4F.)	1.65±0.15	8.02±0.38	25.26±2.05	342.7±39.9	211	212

second group was fed a diet containing 0.2 per cent thiouracil and the third group was fed a diet containing 0.03 per cent protamone. With the termination of each study (i.e., the 3-day study, the 6-day study, etc.), all 3 groups were autopsied.

The gland weights obtained in this study are given for the males and females of each group in Table XXVI. In most instances, there was no marked difference between the relative gland weights for the males and females of all control groups. Generally, the adrenals of the males weighed slightly more than those for the females. On the other hand, the thyroids for the males were usually somewhat smaller. For some reason, the bursae of the control males in the 6-day study averaged about 80 mg. less in weight/100 gm. of body weight than the weight of this gland for the control females.

After 3 days on thiouracil, the males were found to possess larger adrenals, smaller bursae, and slightly smaller thyroids than the females. But after 6 days of feeding thiouracil, the reverse situation was indicated. Following 9 and 12 days of thiouracil administration, it was indicated that the bursae were smaller for the males than for the females.

It was found that the adrenals of the males administered protamone for 3 days were heavier than for the females by an average of about 1 mg./100 gm. of body weight. For all periods of protamone administration, the smaller spleens were possessed by the males. With the exception of the 6-day study, a similar observation was made with respect to the bursae. After 12 days on protamone, there was an

TABLE XXVI

THE EFFECT OF INDEPENDENTLY ADMINISTERING THIOURACIL AND PROTAMONE FOR 3, 6, 9, AND 12 DAYS ON THE AVERAGE GLAND WEIGHTS OF NEW HAMPSHIRES

(Trial 15)

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pituitary	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
3 day study							
Control:							
Males (10)	1.11± 0.10	6.18± 0.40	13.16 ± 0.65	521.3 ± 37.2	227.1 ± 19.7	391	440
Females (10)	1.01± 0.03	6.27 ± 0.43	12.14 ± 0.69	509.7 ± 23.5	234.0 ± 16.5	356	392
Thiouracil:							
Males (10)	1.08 ± 0.07	6.55± 0.29	16.12 ± 1.59	339.8 ± 36.3	211.0± 31.4	395	411
Females (9)	1.16 ± 0.06	8.15 ± 0.41	14.97 ± 1.30	443.0 ± 81.6	221.0 ± 28.4	359	358
Protamone:							
Males (10)	1.07 ± 0.05	5.08 ± 0.24	13.03 ± 0.40	511.2 ± 43.9	249.9 ± 13.6	393	451
Females (10)	1.06 ± 0.07	5.86 ± 0.43	12.02 ± 0.64	537.9 ± 40.1	302.8 ± 37.7	355	407
6 day study							
Control:							
Males (10)	1.05 ± 0.08	6.51 ± 0.58	11.46 ± 0.56	447.7 ± 23.1	270.2 ± 27.0	393	521
Females (10)	1.09 ± 0.09	8.21 ± 0.73	10.71 ± 0.55	530.3 ± 32.2	283.4 ± 18.3	355	460
Thiouracil:							
Males (10)	1.14 ± 0.06	11.50 ± 0.93	12.53 ± 0.84	469.0 ± 33.9	231.8 ± 24.2	394	506
Females (10)	1.18 ± 0.06	10.07 ± 0.57	13.48 ± 0.59	391.6 ± 38.2	279.5 ± 35.8	354	428
Protamone:							
Males (10)	0.90 ± 0.06	4.63 ± 0.45	11.35 ± 0.63	523.0 ± 42.5	228.7 ± 15.1	393	532
Females (10)	0.99 ± 0.05	5.78 ± 0.44	10.90 ± 0.37	498.4 ± 46.9	290.0 ± 17.2	355	469

TABLE XXVI, Continued

THE EFFECT OF INDEPENDENTLY ADMINISTERING THIOURACIL AND PROTAMONE FOR 3, 6, 9, AND 12 DAYS ON THE AVERAGE GLAND WEIGHTS OF NEW HAMPSHIRES

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Gms.	
	Pituitary	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
9 Day Study							
Control:							
Males (10)	1.00 ± 0.05	5.72 ± 0.29	10.99 ± 0.82	471.5 ± 25.5	193.6 ± 13.0	392	577
Females (10)	0.98 ± 0.04	6.75 ± 0.40	10.69 ± 0.57	480.9 ± 43.2	249.7 ± 20.6	355	506
Thiouracil:							
Males (9)	1.00 ± 0.05	16.74 ± 1.90	10.48 ± 0.47	373.1 ± 15.3	208.1 ± 15.1	390	580
Females (10)	1.08 ± 0.05	16.53 ± 1.18	10.93 ± 0.66	431.1 ± 37.4	219.1 ± 13.2	354	500
Protamone:							
Males (10)	0.98 ± 0.08	3.62 ± 0.35	11.80 ± 0.62	443.8 ± 33.7	220.2 ± 17.4	392	584
Females (10)	0.91 ± 0.05	4.36 ± 0.37	10.40 ± 0.67	542.0 ± 36.2	251.7 ± 17.8	355	512
12 Day Study							
Control:							
Males (10)	0.93 ± 0.03	5.69 ± 0.48	9.38 ± 0.48	533.7 ± 32.1	208.9 ± 19.1	394	649
Females (10)	0.98 ± 0.05	6.81 ± 0.56	9.99 ± 0.63	502.0 ± 28.8	239.9 ± 18.4	355	566
Thiouracil:							
Males (10)	1.09 ± 0.11	21.22 ± 4.15	10.31 ± 0.43	332.1 ± 27.2	175.0 ± 11.4	394	627
Females (9)	1.05 ± 0.06	19.46 ± 2.38	10.12 ± 0.40	379.6 ± 34.0	181.6 ± 12.5	355	549
Protamone:							
Males (10)	0.82 ± 0.04	3.63 ± 0.21	11.73 ± 0.50	442.8 ± 29.8	187.2 ± 13.7	422	667
Females (10)	0.96 ± 0.05	4.22 ± 0.34	10.45 ± 0.50	484.7 ± 40.0	238.2 ± 8.2	355	585

indication that the adrenals were slightly larger in the males.

Of interest was the large variation in adrenal weights for the birds fed thiouracil for 3 days. The standard error for the weights of this gland progressively decreased as the birds were given thiouracil for longer periods. It was noted that the 10 birds showing negative weight gains at the end of 3 days on thiouracil feeding had larger adrenals (18.45 mg./100 gm. of body wt.) than the 9 birds showing positive weight gains (12.37 mg./100 gm. of body wt.).

In figure 13, the percentage by which the various glands of the birds fed thiouracil and protamone deviated in weight from the control has been plotted. The observations for the males and females of each group have been combined. It is interesting to note that for a given experimental period, protamone generally has had the opposite effect of thiouracil. The pituitary of the thiouracil groups is larger than the control for all occasions, while this gland is smaller for the protamone groups except at 3 days. The adrenals of the former groups increased in weight during the first period of the trial, then decreased. This gland for the latter groups showed no change until the twelfth day when an increase in weight was noted. The spleens and bursae weighed less in the birds administered thiouracil for all periods. An increase in the weight of these glands was noted during the early periods of protamone feeding followed by a slight decrease in weight at 12 days. The thyroids of the groups fed protamone progressively decreased in weight as the study proceeded. Conversely, the thyroids of the groups administered thiouracil increased in weight. The bursa and spleens of the thiouracil-fed birds

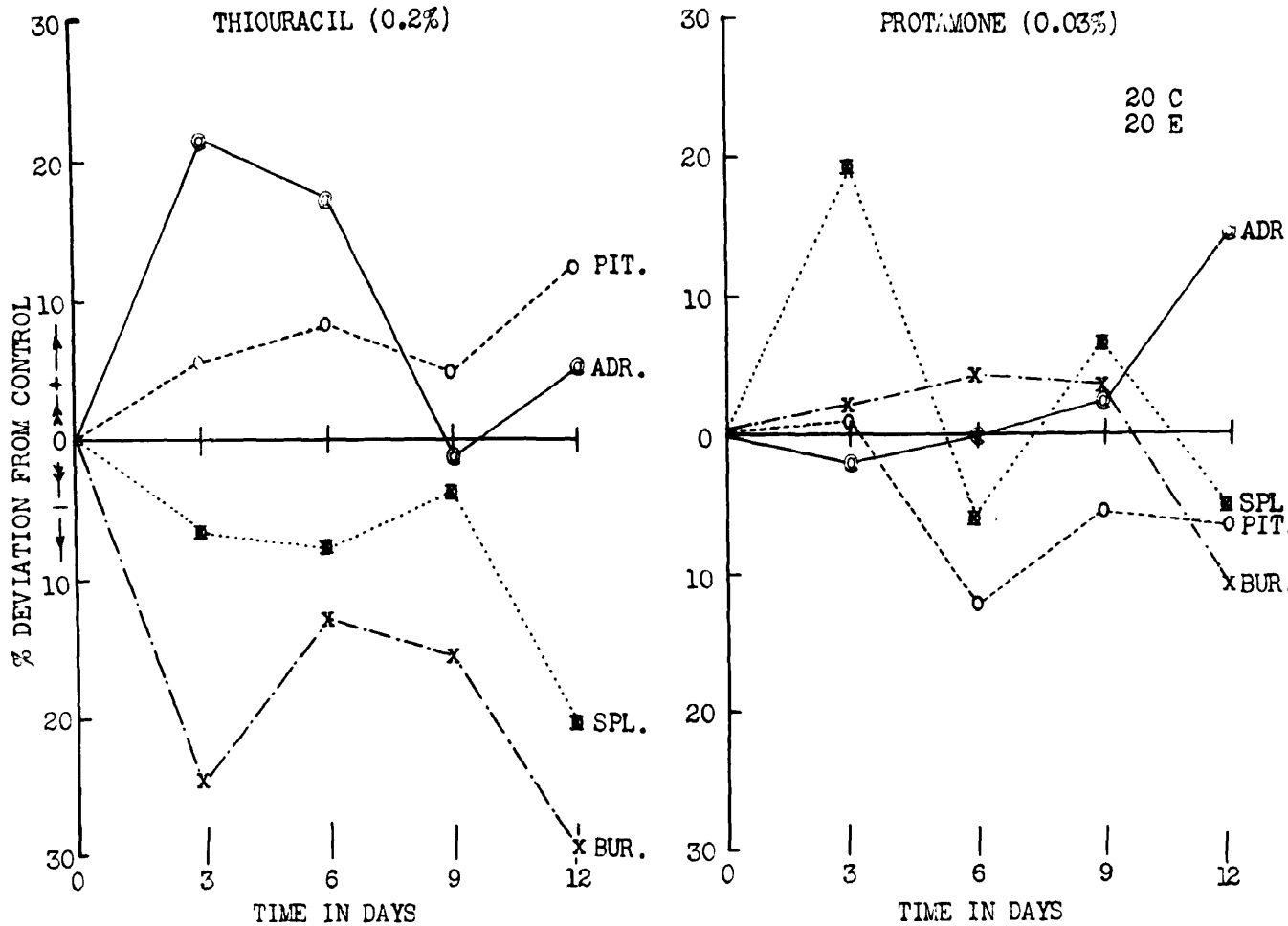

Figure 13. The per cent deviation from the control in the gland weights of New Hampshires independently administered thiouracil and protamone for periods of 3, 6, 9, and 12 days.

seemed to recover in weight during the sixth and ninth days of the study. These recoveries were coincident with the first marked hypertrophy of the thyroid.

The growth rate of birds fed protamone seemed to be increased. Thiouracil adversely affected the growth rate.

Trial 16

This study was conducted to determine if there were a difference in the response shown to thiouracil by New Hampshires as compared with White Leghorns. For this purpose two comparable groups were selected from each breed. Each group contained 8 males and 8 females. During a period of two weeks, one group of New Hampshires and one of White Leghorns were administered thiouracil at a level of 0.2 per cent. The study was then terminated and all four groups were autopsied.

The main gland of consideration in this study was the thyroid gland. But the results presented in Table XXVII show that there is no marked difference in the two breeds with regard to the observed thyroidal hypertrophy as a result of feeding thiouracil. It was noted that on a relative basis, the adrenal weights of the control Leghorns were larger than the weights of this gland for the control New Hampshires. The weight decreases observed for the adrenals, bursae, and spleens of the two groups fed thiouracil were similar.

TABLE XXVII

THE EFFECT OF FEEDING THIOURACIL (0.02%) FOR 2 WEEKS ON THE GLAND WEIGHTS OF NEW HAMPSHIRES AND WHITE LEGHORNS

(Trial 16)

GROUP	Weight in mg./100 gm. of Body Wt.					Body Wt., Grams	
	Pituitary	Thyroid	Adrenal	Bursa	Spleen	Initial	Final
New Hampshires							
Control:							
Males (8)	0.90± 0.04	6.78± 0.99	10.23±0.38	523.0± 30.5	227.5± 29.3	387	656
Females (8)	0.92± 0.05	7.48± 0.69	11.19±0.40	510.0± 58.1	219.8± 21.1	358	602
Experimental:							
Males (8)	0.98± 0.06	23.88± 1.78	9.78± 0.56	266.8± 33.1	155.4± 10.9	390	658
Females (7)	0.89± 0.08	19.67± 2.36	9.30± 0.45	379.5± 40.1	181.2± 14.2	365	632
White Leghorns							
Control:							
Males (8)	1.06± 0.06	5.66± 1.09	13.99± 0.43	531.5 ±43.2	221.8± 8.5	297	477
Females (8)	0.99± 0.06	7.33± 0.64	13.45± 0.74	586.9 ± 58.5	250.7 ± 15.6	269	430
Experimental:							
Males (8)	1.04± 0.07	20.31± 3.71	11.37± 0.91	386.8± 43.5	151.7± 13.8	298	492
Females (8)	1.07± 0.09	19.14± 2.56	13.32± 0.92	311.1± 38.1	196.6± 22.1	269	422

DISCUSSION

Before proceeding with a discussion of the results of this study, a few statements should be made concerning some of the experimental equipment and techniques employed. The revolving cages used in the muscular fatigue phase of this study, while being satisfactory, were by no means perfect. It was found that the power of the motor was too low to permit the revolving of birds over 6 or 7 weeks of age. The wire mesh was found to be injurious to the feet of the individuals which required an extended period of time to exhaust. This latter situation could possibly be corrected by constructing cages of a wire mesh which had been coated with a durable covering of rubber. A number of cages would be desirable if one plans extensive studies of this type. Ideally all the cages used should have a central power source. This arrangement would facilitate the problem of synchronization.

The forceps shown in figure 6 were extremely useful for removing the adrenal and pituitary glands during autopsy. It was observed that the adrenals of the chicken were so intimately associated with the other tissues of the area that an instrument of this type was essential if the glands were to be removed quickly and completely. Besides the chicken and the turkey, the writer has removed adrenal glands from the rat, the rabbit, and the turtle. Only the turtle has been found to have adrenals which were more difficult to remove than those of the chicken and turkey.

The results of this study have created a great many more questions than have been answered. Since the problem dealt primarily with morphological changes, one can only speculate from these changes what physiological phenomena may be occurring. It has been shown in the foregoing trials that the morphological changes elicited by a number of different stress stimuli are similar. In addition, it has been shown in trials 10, 14, and 15 that the period of time which an animal is subjected to a given stress condition greatly influences the degree or even the type of morphological change noted. Generally speaking, the most prominent changes observed for chickens under stress were those of adrenal hypertrophy accompanied by an involution of the bursa of Fabricius and spleen with a reduction in body weight. It is believed that this is the first occasion that an involution of the bursa under conditions of stress has been reported. The function of this gland has long evaded solution. Perhaps its role in the antibody formation should be considered. Probably it would not be unreasonable to assume that the lymphatic involution observed in the experiment was the result of adrenal hyperactivity. In the review of literature, a number of studies were cited which would lend support to such an assumption (Selye, 1936 a, b; Simpson, et al, 1943; Stoerk, 1944; Antopol, 1950; and Molomut, et al, 1950).

No discernible weight changes were noted for the thyroid glands in most instances except the trials involving exposure to cold and the trials where thiouracil was administered. It was interesting how this gland of birds in cold (trial 10) at first decreased, then increased, and finally decreased in weight. This observation suggests

that the release of the thyroidal hormone during the first week of exposure may account for the initial decrease. Lack of sufficient thyroxin in the circulating blood may account for the thyroidal hypertrophy noted at the end of the third week in cold. The secondary decrease in weight after four weeks of exposure may indicate a decrease in the need for thyroxin, in these older birds, or it might possibly be indicative of a breakdown of their resistance to cold. It was noted that the relative adrenal weights were less at this point also. The final body weights of these animals were not indicative, however, of a breakdown in resistance. There were a few instances in the present experiment where it was suggested that the thyroid hormone might be exerting a growth promoting effect on the lymphatic tissues. Previously the work of Marder, (1949) was cited; a study in which thyroxin was found to increase the weight of lymphatic organs. In trial 15, it was indicated that protamone administration, during the period prior to adrenal hypertrophy, caused slight increases in the weight of the bursa and spleen. These glands of birds subjected to cold in trial 10 and thiouracil in trial 15 markedly decreased in weight in the first period of the study. When the first thyroidal hypertrophy became apparent in these trials, the bursa and spleen seemed to recover somewhat in weight. If a high thyroxin level does cause proliferation of the lymphatic tissue, the weight increase of the bursae for the low-thiouracil-response males subjected to cold in trial 11 may be indicative of a high circulating level of thyroxin. However, this observation was made with only 5 males in the control and experimental group.

It was shown that prolonged conditions of stress usually resulted in hypertrophy of the pituitary. Perhaps the two most striking examples of this observation was the progressive increase in pituitary weight for the birds exposed to cold in trial 10 and thiouracil administration in trial 15. Possibly this hypertrophy was indicative of hyperactivity. Protamone administration in trial 15 seemed to cause a slight reduction in pituitary weight after 6, 9, and 12 days of administering this drug. Was the reduction in weight caused by lessened activity of the pituitary when there was no longer need for it to produce thyrotrophin or was it releasing larger quantities of the other hormones? As will be recalled, Deane and Greep proposed that there was an increased output of ACTH in hyperthyroidism. It was suggested in trial 12 that the pituitary weights were less for birds subjected to fatigue and to high altitudes intermittently and to cold continuously during a period of 24 hours. This observation might indicate a sudden release of pituitary hormones. Histological considerations of this gland from birds subjected to the above stress stimuli might reveal more definitely its state of activity at the time of removal.

It was shown in Phase III of this study that only a short period of stress was sufficient to cause weight changes in the glands and organs considered. After one hour of exposure to simulated altitudes of 12,000 to 15,000 feet, an increase in the weight of the adrenals was indicated while the bursa and spleen decreased in weight. It would appear from trial 14 that the adrenal increased in weight after one hour at high altitudes, returning to normal after 2, 3, and 4

hours of exposure and increased in weight again after 5 hours. This observation might suggest that the adrenals are rapidly acquiring constituents from the blood stream during the first hour. Then increasing demands for the cortical hormones results in a release of greater quantities of these substances; thereby causing a decrease in weight. Continuing demands for the hormones results in greater hyperactivity, perhaps accounting for the secondary hypertrophy noted. Of course the increase in adrenal weight noted at one hour was not pronounced. The rather marked reduction observed in spleen weight after the first hour of exposure was probably caused by a sudden release of red blood cells into the blood stream. These additional cells may have been released because of an acute anoxia at this condition.

There was an abundance of evidence to indicate that the sexes differed in their responses to stress. Morphologically, the most consistent difference in most studies took the form of greater adrenal hypertrophy for the males. This difference was markedly demonstrated in trial 12. The average adrenal weights for the control males of each trial were practically always slightly greater than those for the females. Possibly the greater resistance of the male to fatigue can be attributed to a greater activity potential of the male's adrenal. The observation that the male usually had the larger adrenals is of interest, since for most animals the female has been reported to have larger adrenals (Selye, 1949).

It was rather amazing that such an extreme degree of variation existed among the birds with respect to the number of revolutions required to cause exhaustion. The scope of the present study was too

narrow to consider all the factors probably responsible for this variation. There was ample evidence to suggest that the individuals possessing the largest adrenals were the most resistant birds to fatigue. However, the skeptic might justifiably question whether the adrenal hypertrophy was the cause or the effect of prolonged periods of revolving in the cages. A number of studies have been cited previously which revealed that the adrenal hormones influence an animal's resistance to stress stimuli (Ungar, 1947; Nezamis, 1949; Thorn, et al, 1945; Kottke, et al, 1948; and Ingle, 1944). Therefore, it might be concluded that the adrenal hyperactivity was a contributing factor to the observed fatigue resistance. In trial 9, it was seen that the adrenal hormone, cortisone, failed to favorably affect the resistance of the chickens to fatigue. As a matter of fact, there was an indication that the cortisone had a detrimental effect. There is the possibility that this hormone interfered with the production of other essential adrenal hormones through its action on the pituitary (Selye and Dosne, 1942). Also there is the possibility that the dosage levels used were too high for favorable effects. However, there was no strong evidence to suggest that the doses used were toxic. No pronounced reductions in body weight were noted. The mild convulsions observed in the birds injected with this hormone propose an unusual question which may merit further study.

There was evidence that protamone caused an increase in the resistance of birds to fatigue. But was the action of this drug direct or indirect? It was shown in the last period of trial 15 that protamone administration caused hypertrophy of the adrenals. Earlier, it

was mentioned that Maqsood, (1951), and Deane and Greep, (1947) found that thyroxin stimulated adrenal cortical activity. Wallach and Reineke, (1949) reported that the adrenals of hyperthyroid rats secreted larger quantities of the adrenal cortical hormones. So it might well be that protamone had an indirect effect through its action on the adrenal cortex.

Testosterone implantation seemed to enhance the resistance of the birds during the last period of trial 9. It was necessary to conclude this trial because the birds became too large for the cages. Ideally, it should have been continued for a few more days. Several investigators have been cited who reported that the male hormone exerts an influence on the adrenals (Peczenik, 1944; Leathem, 1944; Selye, 1940; and Langley, 1942). So again it is not possible to state definitely whether this hormone has had a direct or an indirect action in its influence on the individual's resistance to fatigue.

Thiouracil markedly reduced the resistance of chickens to fatigue, possibly because of its affect of the available thyroxin. An unusual observation was that the males retaining the greatest resistance to fatigue subsequent to thiouracil administration also had the largest thyroids (trial 7). Since thyroid hypertrophy was involved and since protamone was shown to enhance resistance to fatigue (trial 9), this observation suggests that the available thyroxin might have been greater for the resistant individuals. While a similar observation was made for the females, it was not nearly so pronounced as for the males. This result may indicate that a high level of thyroxin in the resistant males permitted near-normal functioning of the testes and subsequently

greater androgen secretion. Such an explanation would depend, of course, upon the male hormone causing a greater resistance to fatigue as was suggested in trial 9. No explanation can be given for the lack of a marked difference between the fatigue resistance of the high- and low-thiouracil-response strains of trial 8 after thiouracil administration. An explanation might be found in the fact that all the birds of trial 7 had shown a marked resistance to fatigue prior to being placed on thiouracil. This procedure undoubtedly eliminated those individuals lacking resistance to fatigue for one or several reasons. The reader is reminded, however, that the single individual which retained the greatest resistance to fatigue also possessed the largest thyroid gland.

A correlation was expected to be found between an individual's resistance to fatigue and its subsequent response to thiouracil. But such an observation was not made under the conditions of the study reported in trial 6. There is the possibility that the trial was not extensive enough to establish the true resistance of birds to fatigue prior to placing them on thiouracil. It might be fruitful to repeat the investigation, using several periods of revolving to establish the high- and low-fatigue-resistant groups.

The turkey was much more resistant to fatigue than the chicken. There may be several reasons for this observation. First, the turkey possesses a definite anatomical advantage over the chicken. Its legs are longer, enabling it to take longer and less frequent steps. The turkey was also able to retain its balance in the cages more effectively than the chicken. Interestingly, the absolute endocrine gland

weights for the two groups did not differ appreciably. Of course, since the chicken was smaller, the endocrine gland weights were relatively less for the turkey. Since the turkey has a greater growth rate and a greater resistance to fatigue than the chicken, this observation might suggest one of the following: (1) that a smaller quantity of the hormones produced by these glands is required per 100 grams of body weight for the turkey because the tissues of the turkey are more responsive to the hormones, or (2) that the glands of the turkey produce the hormones more efficiently and at a greater rate.

While the results of this study were not such as to warrant a definite statement that genetic differences exist in the stress response, sufficient positive observations were made to recommend additional studies in this direction. The high-thiouracil-response-strain seemed more resistant to fatigue than the low-response-strain, but this difference was not statistically significant. It is proposed that additional studies of this type be continued when the two strains have been more definitely established. There was no pronounced difference between the Leghorns and New Hampshires in their response to muscular fatigue or thiouracil administration. However, the results indicated that the Leghorns as a group might be slightly more resistant to fatigue than the New Hampshires. Two strains of rats were developed by Rundquist, (1933) differing in their voluntary activity. Brody, (1942) found that by the F_{15} generation, the average distance run by "active" male rats was approximately 35 times as great as the distance run by the "inactive" strain. The females of

the "active" strain ran about 10 times as far as the females of the "inactive" strains. Undoubtedly in developing strains of chickens differing in resistance to muscular fatigue, it will be found that a number of inherited characteristics are responsible for the differences.

It may be that more research needs to be done which considers not groups of animals, but which considers individuals. Ingle, (1952) remarked, "Individual variation in biologic responsiveness may aggravate the investigator to regard it as an impediment to research, but it remains as a dimension of metabolic problems which, for the endocrinologist, extends from the cyclostome to man and within the species encompasses the individuality of both the heterozygous and enzygotic organism." In the present study, a great deal of individual variation was shown to exist not only in the time required to induce muscular fatigue, but also in the time required to cause morphological changes in the glands studied. It was noted in trial 15 that about one-half of the individuals fed thiouracil for 3 days showed negative weight gains. As will be recalled, the adrenals of these individuals were larger than those for the birds showing positive weight changes. Possibly this observation suggests that the level of thyroxin was less for the former individuals and its production was more effectively blocked by thiouracil feeding. Or it may indicate that the thyroids of these individuals were slow in responding to the thyrotropic hormone or that their pituitaries were slow in producing this hormone. Whatever the cause, thiouracil administration seemingly constituted a greater stress stimuli for these individuals. Another

instance of pronounced individual variation was the short cold study of trial 14. Certain individuals responded with marked increases in the weights of the adrenals while others displayed no increase. No less phenomenal was the extreme variation in individual resistance to fatigue which has already received passing mention. For example, just why certain individuals required as long as 12 hours to exhaust at 22 r.p.m. while others required only 2 minutes is not completely clear. Nor is it known why the fatigue resistance of one individual of trial 9 was not adversely affected by cortisone injections. On the contrary, it was more resistant than any other individual, control or experimental. The observation that certain individuals seemed unable to adapt themselves to cold or thiouracil administration may be worthy of additional investigation. These individuals became emaciated and died a short time after the study was begun.

While the writer believes the hormonal aspect of this problem to be an important one, it is not believed to be the complete answer to the problem. For example, with regard to muscular fatigue, such physiological factors as: (1) respiratory efficiency as perhaps influenced by permeability of the membranes, vital capacity of the lungs, possibly by some impediment to breathing, and perhaps even the individual O_2 and CO_2 saturation curves; (2) circulatory efficiency as affected by heart volume, blood pressure, and the condition of the blood vessels; (3) muscular development; (4) anatomical structure; and (5) metabolic rate. With regard to the last factor, heat elimination might be an important consideration. Garren and Craig, (1952) observed that the voluntary tolerance limits of exercising subjects were related in a

hyperbolic manner to their rate of heat storage. Concerned also might be the efficiency of the digestive tract, since a number of investigators have been cited who revealed that a number of nutrients are extremely important in an animal's response to stress (see NUTRITION in Review of Literature). In this respect the nutrient, water, may be important. In the present study, the birds at high altitudes and the birds subjected to muscular exercise invariably passed large quantities of water with their feces. Therefore, the problem of water balance may be important in the chickens' response to stress. Even though the chicken is generally believed not to possess a great deal of intelligence, it is conceivable that psychological factors might be involved in some manner. In this respect, the learning capacity of the individual chicken might influence its ability to run in the revolving cages.

In conclusion, it is believed that the results of the present experiment have been promising enough to recommend additional studies of this type with the chicken. Many problems of economical significance to the poultry industry might possibly have their solution in such studies.

SUMMARY

The following stress stimuli were investigated in chickens: muscular fatigue, cold, high altitudes, and protamone and thiouracil administration.

Periodic induction of muscular fatigue caused an enlargement of the adrenals and a reduction in the weight of the thymus, the bursa of Fabricius, and the spleen. Males were more resistant to fatigue and generally had larger adrenals than the females. Genetic differences in the fatigue-response were indicated. The turkey was found to be more resistant to fatigue than the chicken. Thiouracil administration lowered the resistance of chickens to fatigue, the most resistant individuals among the treated birds being those with the greatest thyroid enlargement. Protamone or testosterone treatment seemed to enhance resistance, but cortisone did not.

The adrenals of birds exposed to cold (44° F.) were larger and the bursa and spleen smaller than in birds at room temperature. One and four weeks of exposure caused a decrease in thyroid weight, but three weeks of exposure caused an increase.

Chickens placed at simulated altitudes of 12,000 to 15,000 feet for one to two hours had larger adrenals and smaller bursae and spleens than control birds. These changes were augmented with four and five hours of exposure.

Thiouracil and protamone were administered independently for periods of 3, 6, 9, and 12 days, respectively. Thiouracil for 3 to

6 days increased adrenal weight, but continued treatment decreased adrenal weight. The bursa and spleen of thiouracil-treated birds were smaller for all periods of treatment than in the control birds. Protamone caused a progressive enlargement of the adrenals, and initially caused an enlargement of the bursa and spleen which was followed by a decrease in the size of these organs.

There was an indication that protamone administration caused a reduction in pituitary weight. Prolonged periods of exposure to the other stress stimuli usually caused hypertrophy of the pituitary.

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Doctor of Philosophy, 1953

Date of Birth: April 2, 1925

Place of Birth: Hendersonville, North Carolina

Secondary Education: Etowah High School, Etowah, North Carolina
Hendersonville High School, Hendersonville, North Carolina

Collegiate Institutions Attended	Date	Degree	Date of Degree
University of North Carolina	June, 1944	A. B.	June, 1947
North Carolina State College	Sept., 1947	B. S.	June, 1949
University of Maryland	June, 1949	M. S.	June, 1951
University of Maryland	June, 1949	Ph.D.	Feb., 1953

Publications: The Effect of Temperature and Time of Storage on the Fertilizing Capacity of Undiluted Fowl Semen.

The Response of Young New Hampshire Chickens to Conditions of Stress (Abstract).

Positions Held:

Lieutenant (jg) U.S.N.R.

Farm Supervisor in Pender County, North Carolina

Graduate Assistant in the Poultry Department of the University of Maryland

Physiologist, Applied Physiology Branch, Medical Laboratories, Army Chemical Center, Maryland