COMPARATIVE EFFECTS OF THYROIDECTOMY AND THIOURACIL ADMINISTRATION ON THE GROWTH AND DEVELOPMENT OF DOGS

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COMPARATIVE EFFECTS OF THYROIDECTOMY AND THIOURACIL ADMINISTRATION ON THE GROWTH AND DEVELOPMENT OF DOGS

By

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INTRODUCTION

Since the late 1800's, when physiologists first became interested in the thyroid gland and its function, there has been more interest and research in this phase of endocrinology than any other.

Thyroid function has been studied quite thoroughly in most species of experimental animals and in man. If one is to review the literature on this subject he will find differences in reaction of the various species to experimentally induced hyperthyroid and hypothyroid states. The study of thyroid function resolves itself into more or less of a separate problem in each species. There are similarities of course, but there are also differences among the various species which should be brought out.

The experimental animal employed in this paper, the dog, has been used very little in research along these lines, the probable reason being that this species is inherently quite nervous and does not lend itself well to experiments of a metabolic nature. The dog is not as simple an animal to keep and work with as some of the smaller species.

As a result, literature available on experimental hypothyroidism in dogs is quite meager. From the literature, one might gain the impression that the thyroid is not as essential for normal body function in this species as in others. Dye and Maugham (1929) reported cretinism in the dog following surgical thyroidectomy, but their tables lead one to suspect a smaller change than is represented in the written portion of their work. Mayer (1947) and Glock (1949) are very much in agreement that goitrogen administration produces no change in growth or development of dogs, although both report gross and microscopic evidence of thyroid hypertrophy and hyperplasia.

Clinically, the writer has observed a condition of older dogs which in some respects resembles human myxedema. The animals become overweight and blocky in appearance. The skin is thickened, particularly over the lumbar and gluteal regions, and the hair in these areas becomes sparse and wiry. No edema has been seen. The cases have, for the most part, responded well to thyroid administration.

When the thyroid gland was first noted it was theorized that its purpose was to fill out and lend a smoother appearance to the neck region. Schiff (1884) in his research on thyroid function stated that it seemed quite improbable that an organ with the highly specialized structure of the thyroid would be placed in the body for the sake of appearance.

It seems as though this thought might easily be applied to the thyroid of the dog, in view of the more recent research. With the before mentioned statements in mind, it was decided that clarification of the functional status of the thyroid of the dog might be attained through concurrent study of chemically and surgically induced hypothyroidism.

REVIEW OF THE LITERATURE

Effects of Thyroidectomy

Early studies on the effects of thyroidectomy are somewhat clouded in that the full significance of the parathyroid was not understood at that time, and the results reported in these earlier papers reflect the effects of thyroparathyroidectomy rather than of thyroidectomy alone.

Schiff (1884) was the first to investigate this field. He stated that the removal of the thyroid of the dog almost invariably resulted in death, while in rodents no severe symptoms were noted. These results were confirmed by Horsley (1891) who described nervous symptoms, severe tetany, convulsions, and early fatal termination following thyroidectomy in dogs and other carnivora. This worker was apparently the first to describe the effects of thyroidectomy in ungulata by unwittingly leaving the external parathyroid when operating. These results in dogs have been duplicated by Vincent and Jolly (1905), and Carlson and Woelfel (1910).

Considerable light was shed on this subject by the work of Gley (1891) who first designated the importance of leaving the parathyroid glands intact when removing the thyroid. He found that this procedure resulted in a marked reduction in symptomatology and considered the parathyroid a "helper organ" which could replace the function of the thyroid. With the advent of these findings more attention was given the individual study of these glands.

Effects on Body Weight

The effect of thyroidectomy on the body weight of dogs is described by Dye and Maugham (1929). In dogs which were thyroidectomized at five to six weeks of age a noticeable decrease of weight gain was seen at the end of two weeks following the operation. It was found that frequently the retardation of growth was masked by the excessive deposition of adipose tissue, but that the retardation invariably exceeded the fatty deposition and the weight gain remained adversely affected. Binswanger (1936) presented data which confirms this work. His body weight charts showed somewhat more definite differences.

These findings have been duplicated in other species. Larson (1919: 1920) found significant retardation in weight gain together with unthriftiness in young rats after thyroidectomy. Similar results were observed in this species by Hammett (1922). Salmon (1938) found severe retardation of weight gain in newborn rats which had been thyroparathyroidectomized. She observed that a growth plateau was established at three weeks after the operation, and that while injections of thyroid substance stimulated further growth and weight gain, injections of parathyroid substance gave little response. In sheep and goats, Simpson (1924) reported a distinct retardation of weight gain in animals thyroidectomized at three to four weeks of age. Landauer (1929) reported a general arrest of growth in domestic fowl in three naturally occurring cases of thyrogenous dwarfism. In monkeys, Flieschman, Shumaker and Straus (1943) reported one case in which growth was completely arrested. Considerable drop in weight gain following thyroidectomy in immature guinea pigs has been reported by Silberberg and Silberberg (1940).

The above results were obtained on immature animals. Thyroidectomy in older animals has not shown any demonstrable effect on the body weight as indicated by the work of Simpson (1913) except possibly in the manner of decreased basal metabolic rate and consequent fattening. An initial loss followed by an increase of weight in thyroidectomized mature dogs was reported by Borgman (1949).

Effects on Body Stature and Skeletal Growth

A definite change in body stature and relative growth and development of the osseous skeleton is seen in most cases in which thyroidectomy is performed in the young experimental animal. Dye and Maugham (1929) reported broadening of the head, shortening and broadening of the muzzle, thickening of the neck, and feet, and relatively broader and thicker limbs in young dogs after thyroidectomy. The animals appeared stunted and hump-backed, and showed typical cretinism. Edema was not present in the various parts of the body as observed in human patients suffering from hypothyroidism (Cecil 1946). The effects on dogs were confirmed by Binswanger (1936). In the domestic fowl with thyrogenous dwarfism, Landauer (1929) reported bulging of the eyes and edema of the surrounding tissue accompanied by arrested skeletal development. Simpson (1913) described sheep which had been thyroidectomized at two months of age as having a squat, stunted appearance. Reineke and Turner (1941) reported that goats appeared dull and sleepy, and exhibited a relaxed stance after thyroidectomy at four weeks of age.

The skeletal system seems from all accounts to be severely affected by surgically induced hypothyroidism. The average length of the long bones was less in dogs which were thyroidectomized at four to six weeks of age. There was very little change in the width of the diaphysis of the long bones, but the length-breadth index was considerably greater in thyroidectomized as compared to control animals (Dye and Maugham 1929). Binswanger (1936) also reported this striking difference, particularly in the length of the long bones. He stated that while the normal controls had gained full length of the long bones by nine months of age, the thyroidectomized animals gained as much as 3 cm after this age.

In rats, Hammett (1927) observed the same degree of retardation in both bone growth and body weight. In this work it was found that bone weight remained the same, but that the long bones were considerably shorter in thyroidectomized animals than in controls.

Very little disturbance of the diaphysis of the long bones, but definite delay in the replacement of hypertrophic cartilage cells by bone was reported in immature guinea pigs after thyroidectomy. Proliferation of the cartilage cells was maintained and temporarily increased in some cases (Silberberg and Silberberg, 1940).

In sheep thyroidectomized at two months of age, Liddell (1925) reported the appearance of prognathism at six months of age. He also noted that the skulls were shorter and disproportionately wide in these animals. Reineke and Turner (1941) observed a growth lag in the jaw bones of goats after early thyroidectomy.

It has been found that hypothyroidism may be the cause of some of the deforming bone diseases of children such as Perth'es disease and Osgood-Schlatters disease (Schaefer and Purcell, 1941).

Effects on Dentition

It would be reasonable to assume, in view of the effects of thyroidectomy on the development of bone, that teething might also be affected. Binswanger (1936) stated that secondary dentition in thyroidectomized dogs occurs from one to two weeks later than in normal control animals. With the exception of one case in which the secondary molars did not appear, Dye and Maugham (1929) saw no effect on dentition. Delayed eruption of secondary teeth has been observed in sheep (Liddell, 1925).

Effects on Body Temperature

In dogs, Binswanger (1936) reported an average temperature drop of .3°C following thyroidectomy. The body temperature of adult thyroidectomized dogs averaged only slightly less (.5° F) than prior to the operation (Borgman 1949). Simpson (1913)reported a distinct fall in body temperature after thyroidectomy at two months of age. In his work with cats, Smith (1894) stated that thyroidectomy results in inefficient function of the heat regulatory mechanisms of the animal body.

Effects on Pulse Rate

Binswanger (1936) observed a decrease in pulse rate in thyroidectomized dogs. Borgman (1949) reported a 16% drop in the pulse rate following thyroidectomy of adult dogs. The pulse rate of rats was slowed to fifty to one hundred beats per minute after thyroidectomy compared to a normal of three hundred beats per minute in control animals (Fishbourne and Cunningham, 1938). In thyroidectomized sheep two years of age and over, Simpson (1913) observed only a slight slowing of the pulse. The same worker reported a distinct fall in pulse rate in young, thyroidectomized lambs within two weeks after the operation. Jailer, Sperry, Engle, and Smelser (1944) reported circulation time decreased by approximately 30% in adult monkeys following thyroidectomy. Studies in human beings have revealed correlation of metabolism and pulse rate in children, but the relationship is lost as aging takes place. (Sutliff and Holt 1925).

Effects on Hemopoietic System

The effect of thyroidectomy on the blood of animals is not well established. In dogs, Goldberg and Chaikoff (1952) reported that in two of six dogs thyroidectomized by the use of I^{131} a drop in red cell count of 20% to 30% was seen. The cells in this case appeared hypochromic.

Landauer (1929) in his studies on naturally - occurring thyrogenous dwarfism in fowl found a decrease in the number of bone marrow cells, and in some cases complete replacement of the bone marrow by connective tissue. Macrocytic anemia, with decreased cell volume and hemoglobin was seen in rabbits after thyroidectomy by Kunde, et al (1932).

Effects on Food Intake

Little attention has been given specifically to food intake following thyroidectomy, although it is generally assumed to be less. This is reported specifically in dogs by Borgman (1949).

Effects on General Appearance and Vitality

A distinct lassitude, particularly after seven months of age, and a coarse dry hair coat is described by Binswanger (1936) in thyroidectomized dogs. In his work with the collie, he stated that the ears did not stand in the normal upright manner after thyroidectomy. Goldberg and Chaikoff (1952) reported sluggishness, thickening of the skin and coarse, wiry hair in dogs thyroidectomized with radioactive iodine. Thyroidectomy in sheep resulted in listlessness and a stupid appearance. Falling wool was observed in some cases and in all cases there was a diminution of fleece weight when shorn. Horn growth in sheep and goats was found to be markedly retarded (Simpson 1924). In thyroidectomized rats, Larson (1920) reported unthriftiness and laziness. Landauer (1929) showed this in the domestic fowl.

Thyroidectomy at four to twenty days of age delayed the appearance of mature feathers in the brown leghorn fowl. When mature feathers did appear they showed a decrease in melanin, decrease in barbules and had a tendancy to become long and tapered. (Blivaiss and Domm 1942).

The effects on activity are probably due to a decrease in metabolic rate. The decrease in basal metabolic rate following thyroidectomy has been shown to be quite constant among the species. In the dog a 30% drop in BMR was reported by Borgman (1949). In the rat, a 20% to 30% drop was observed (Mayer and Ransom 1945), while in the pigeon the drop was 27% (Marvin and Smith 1943). Workers on other species have produced similar results.

Effects of Thiouracil Administration

Following the discovery that several naturally occuring materials such as cabbage and rape seed would produce a condition resembling goiter when fed over a period of time, much attention has been given to the inhibition of thyroidal activity by chemical compounds. Astwood (1943 a) compared a number of chemicals by biological methods and concluded that those containing the thioureylene radical produced the greatest effect with the least toxicity. The compound 2- thiouracil was found to be one of the most effective in inhibiting thyroid function.

The effect of these compounds on the thyroid gland is hypertrophy and hyperplasia, with decreased colloid content of the follicles and increased height of acinar epithelium (Mackenzie and Mackenzie 1943).

In studies on the effect of thiourea and sulfonamides on the thyroid of rats, Astwood, et al (1943) determined that the administration of thyroxine inhibited the effects on the gland, and that likewise these effects did not occur in hypophysectomized animals. This work indicated that possibly an overproduction of thyrotrophin was responsible for the gross and microscopic changes in the thyroid of animals treated with goitrogens.

The administration of thiouracil to human patients causes a more rapid uptake of iodine by the thyroid gland and also a very rapid loss (Stanley and Astwood 1947). Franklin, et al (1944) demonstrated that there was less thyroxine and diiodotyrosine in the thyroid of rats after the administration of thiouracil. Thyroglobulin storage was inhibited completely by the administration of thiourea to rabbits (Bauman, et al 1944). These studies show that thiouracil administration results in a definite inhibition of thyroxine formation at the diiodotyrosine level.

Effect on Body Weight

Danowski, et al (1946) reported no change from normal of weight gain in dogs fed thiouracil. In his experiments with beagle puppies, Mayer (1947) reported no differences from control animals in body weight gain between pups fed thiouracil twice daily for the first sixty days of the experiment, then once daily for four months, at the rate of 25 - 30 mg per kilogram of body weight. No obvious difference in growth as measured by body weight was noted in puppies by Glock (1949). The adult dogs which were given thiouracil maintained their body weight as well as the controls.

Williams, et al (1944) demonstrated that thiouracil definitely inhibited the growth of young rats, and that the administration of growth hormone did not reverse this effect. After the administration of thiouracil to rats, Hughes (1944) found growth to be very much inhibited after the first ten days. His control animals ultimately weighed twice as much as those treated. In adult rats fed 1% thiouracil in their diet an average weight loss of 42 gm in twenty to twenty-two days of treatment was recorded by Leathem (1945). Astwood, et al (1945) found a very definite retardation of body weight gain in rats on goitrogenic drugs and used this as a means of estimating the effectiveness of several of these compounds. A loss of weight was reported in adult rats fed .5% thiouracil in the ration (Leathem, 1946). A marked depression of growth was reported by Boatman and Moses (1951) in young rats receiving .5% thiouracil in the diet. Bauman and Marine (1945) reported that rats fed 40 mg of thiouracil daily gained weight at nearly the same rate as normally handled littermates, but that increased dosage caused stunting.

In the chick, Mixner et al (1944) found that .1% thiouracil in the ration for twelve days produced the maximal effect on the thyroid. Lighter, perhaps more hyperthyroid breeds, gave the greater response. Kempster and Turner (1945) noted that .2% thiouracil in the ration of broilers for sixteen days did not influence body weight, food consumption, or economy of gain, but that there was an improvement of finish. In a second trial covering a period of five weeks, it was found that this level of thiouracil produced lower gains, greater food consumption per pound gain and consistently lower grade when slaughtered. In New Hampshire cockerels fed on rations containing .025, .05 and .1 percent thiouracil respectively, Mixner, et al (1946) found a progressive decrease in weight gain as thiouracil was increased. Glazener and Jull (1946) found a depressed growth when .2% thiouracil was given to young chicks in the mash. This is confirmed by Andrews and Schnetzler (1946) who stated that in addition to growth depression there was a greater efficiency of food consumption, and a significant improvement of fleshing and fat deposition in broilers.

The use of .1% thiouracil in the ration of swine has been reported to cause an increase in body weight gain and reduced total food requirement per pound of gain (McMillen, et al 1947). When the administration of thiouracil is started before maturity less weight gain is seen. (Beeson, et al 1947). Swine given .25% thiouracil in the feed gain rapidly at first and then stop gaining, although they consume less feed per pound gain than controls (VanderNoot, et al, 1948). In these studies it was found that the normally active breeds responded more vigorously to this therapy than the breeds which are more docile.

Andrews, et al, (1947) reported a depression of weight gain of .064 to .071 lb per day in lambs, with no difference in feed consumption per pound of gain when feeding .33 gm of thiouracil daily in the ration.

Weight gain in steers was not altered by 4 to 6 gm of thiouracil daily, but there was a slight increase in weight gain and slightly better gain per pound of feed when 2 to 4 gm were administered daily. There was a tendency to improve the dressing percentage and degree of finish at both dosage levels (Beeson, et al, 1947).

McQuillan and Trikojus (1946) found that guinea pigs given 80 mg of thiourea twice daily did not gain weight as fast as controls.

Effects on Body Stature and Skeletal Growth

Studies on the skeletal growth of animals made hypothyroid by the administration of anti-thyroid compounds have not been emphasized in the literature. In most cases it has been simpler to use the body weight as an index of drug activity.

No changes in growth rate or body stature were reported in dogs by Glock (1949) or by Mayer (1947) after administration of thiouracil. Epiphysial fusion was unaltered macroscopically and microscopically in the latter case.

A distinct retardation of skeletal growth in rats was noted by Williams, et al (1944). Likewise, Hughes (1944) showed that the administration of 1% thiouracil in the drinking water of rats caused inhibition of growth and caused persistence of infantile skull proportions. Intermittent (once-weekly) doses showed no effect.

Mixner, et.al (1946) showed that 1% thiouracil produced a distinct decrease in length gains in New Hampshire cockerels. Depression of growth in the body skeleton of the chick was seen after the administration of .2% thiouracil in the feed (Glazener and Jull 1946).

In their work on swine, McMillen, et al (1947) showed that there was possibly a slight decrease in skeletal growth in animals fed .1% thiouracil in the ration for a period of forty-one days. A concentration of .25% thiouracil caused a more rapid gain for the first ten days, but almost a cessation of skeletal growth after that time (VanderNoot, et al 1948). Very definite retardation of growth, causing a short, "chuffy" appearance in swine fed for six weeks on .1% thiouracil was seen by Beeson, et al (1947).

<u>Effects on Body Temperature</u>

Although specific study of the body temperature as influenced by thiouracil administration has not been attempted, it is assumed that the effect would be depression as reported following surgical ablation of the thyroid gland (Salmon 1938). A lower body temperature was noted by Hughes (1944) in rats fed 1% thiouracil in their drinking water.

Effects on Pulse Rate

Leblond and Hoff (1944) fed thiourea to rats over a four month period and produced a reduction of heart rate from 313 to 218 per minute.

Effects on Food Intake

Leathem (1945) found that the daily food consumption of rats fed .1% thiouracil remained normal for ten days and then was slightly below normal. In rats given .1% thiouracil in drinking water no change in quantity of food consumed was noted (Rawson, et al 1944).

Much more research has been done on meat-producing animals in which case the ratio of weight gain to food consumption is an important factor. In broilers fed .2% thiouracil in the ration for sixteen days no influence on food consumption or economy of gain was noted by Kempster and Turner (1945). They found, however, that over a longer period of time (five weeks) food consumption per unit gain increased. Mixner, et al (1946) reported an increased gain, while food consumption decreased in cockerels fed .025, .05 and .1% thiouracil in their mash. These findings are born out by Andrews and Schnetzler (1946) who noted greater efficiency of food consumption in broilers fed on the same percentages of thiouracil for a period of eight weeks.

In swine, McMillen, et al (1947) showed that feeding a ration containing .1% thiouracil reduced total feed requirement per unit gain. This is substantiated by the work of VanderNoot, et al (1948).

Andrews, et al (1947) reported no change in feed consumption per unit gain in lambs fed .25 to 2 gm of thiouracil daily. Steers fed 4 to 6 gm of this compound daily for fifty-four days showed a slightly increased gain per pound of feed (Beeson, et al 1947).

Effects on the Hemopoietic System

In dogs fed thiouracil, Mayer (1947) found no significant change in the blood picture except in two experimental animals which showed high relative lymphocyte counts (60%+). A mild anemia, averaging three million less red blood cells, has been reported in rats fed .1% thiouracil in their diet for a period of one hundred and fifty days. Leucopenia was observed in some cases, but this finding was not constant (Leathem 1945). The administration of .2% thiouracil in the feed resulted in granulocytopenia, lymphocytosis and reduced red blood cells and hemoglobin (Gordon, et al 1945).

Warren (1945) studied the effects of thiouracil in vitro and found that when 100 mg % thiouracil was added to autogenous neutral serum the respiration of bone marrow placed in the serum was reduced. He notes that the compound has an affinity for the myeloid cells, particularly the more immature, but that the erythroid elements are disturbed very little.

Many more reports of maleffects of thiouracil on the blood have been reported in the human being due to its use in treatment of clinical thyrotoxicosis. Kahn and Stock (1944) reported a case of fatal agranulocytosis which developed after the administration of 30.8 gm of thiouracil over a fifty-four day period. In one patient showing anemia, leucopenia and complete agranulocytosis the effect on the bone marrow was apparently irreparable (Gargill and Lesses 1945). Williams, et al (1944) found no ante-mortem or post-mortem abnormalities in six patients fed 6 gm of thiouracil daily for twenty-eight days. A marked lowering of the granulocytic cells was noted in 20% of human patients on thiouracil and 2% showed complete agranulocytosis (Fishberg and Vorzimer 1945). In clinical patients being treated for thyrotoxicosis, toxic reactions to thiouracil were noted in 14.5%, and 1.2% showed agranulocytosis (Williams et al 1946). Other untoward reactions are seen such as fever, skin rash and adenopathy, but the agranulocytosis is the dangerous symptom, usually indicating a fatal termination (Bierwaltes and Sturgis 1946).

General Effects

The effect of thiouracil on the integumentary system seems to be much the same as that of thyroidectomy. Hughes (1944) reported a delay in the development of the adult coat in rats. No effect on pigmentation or hair growth was noted by Dieke (1947) after thiourea administration, although phenylthiourea and alpha-napthyl thiourea caused inhibition of both.

Beeson, et al (1947) reported thickened skin and dull, coarse hair in swine fed .1% thiouracil in the ration for six weeks. Comb growth in cockerels was adversely affected by thiouracil administration (Mixner, et al 1946), as was feather pigmentation (Juhn, 1944).

Sluggish reflexes and awkward muscular movements were noted in rats which were given thiouracil (Hughes 1944). McMillen, et al (1947) noted this effect in swine.

Thiouracil reduced the basal metabolic rate of rats 23% when given at the rate of .1% in the drinking water (Reineke, et al 1945). McCartney and Shaffer (1949) found that chicks given .1% thiouracil in the ration required 16% less oxygen. In human patients, Astwood (1943 b) showed that the administration of .2 to 1 gm of thiourea twice daily gave relief from the symptoms of thyrotoxicosis and caused the basal metabolic rate to return to normal. Dosage of .8 gm daily to a patient suffering with thyrotoxicosis lowered the basal metabolic rate from + 64 to + 10 in four days. When an attempt was made to withdraw the drug, the rate again increased (Kahn and Stock, 1944).

Attention is drawn to the marked similarity between the effect of thiouracil administration and that of thyroidectomy.

I^{131} Uptake in Experimental Hypothyroidism

The work of Hertz, et al (1938) opened the way for further intensive study of thyroid physiology. The normal thyroid was found to collect more radioactive Iodine than do other tissues. The administration of thiocyanate or the feeding of cabbage to rabbits was found to cause an increased affinity of the hyperplastic gland for iodine (Hertz, et al, 1940).

Morton, et al (1943) reported that the completely thyroidectomized rat was still able to convert iodide to diiodotyrosine and thyroxine. By chemical analysis they determined that ninety-six hours after the injection of radio-active iodine into thyroidectomized animals 30% of this material present in the liver and small intestine was protein-bound; 20% being found in the diiodotyrosine fraction and 8% in the thyroxine-like fraction.

There has been considerable study of iodine metabolism in the thyroid as influenced by the various anti-thyroid compounds. Franklin, et al (1944) found that thyroids removed one day after the feeding of thiouracil for one week, contained only 12% as much thyroxine as controls, and that this condition persisted to a progressively smaller degree for about two weeks at which time the amounts of labeled thyroxine and diiodotyrosine in the gland had returned to normal. An average of only 10% of a tracer dose of radioactive iodine was concentrated by the thyroid gland of rats given .1% thiouracil daily in their drinking water after twenty-eight days while controls took up an average 56%. Rawson, et al,(1944), indicated that apparently the thiouracil blocked the uptake of radioactive iodine by the gland. In an attempt to gain confirmatory evidence on the efficiency of the thiourea group of goitrogens, Stanley and Astwood (1947) injected radioactive iodine into human patients being treated with thiourea and found that while the controls took the iodine up more slowly, gaining a plateau at twenty-four to forty-eight hours and then remaining constant for some time, the thiourea-treated patients showed a very rapid uptake of radioiodine by the thyroid, but did not retain a plateau for over thirty-six hours. McGinty, et al, (1948) found that eight hours after a single injection of thiouracil rats showed partial escape from the drug, as indicated by the use of radioactive iodine as a tracer. In chicks, on the other hand, it was twenty-four hours before this partial escape was noted. Rawson, et al (1948) noted that rats which had been fed .2% thiouracil in the ration for a period of time took up only about 1/10 to 1/5 as much I^{131} as control animals. The thyroids in this case were examined four hours after the I^{131} injection. Only a slight difference in the amount of I^{131} concentrated in the thyroid gland of rats given thiouracil and controls is noted at a short period (three hours) after injection (Boatman and Moses 1951). In rats which received a tracer dose of I^{131} forty-eight hours prior to the administration of 1% thiouracil in the drinking water, Albert and Tenney (1951) report 50% excretion of radioactive iodine daily, while the normal rate is 8-9% daily.

Cell Plasma Ratios of Radioactive Iodine

In research on the permeability of cell membranes of human red blood cells, Rall, et al (1950) concluded that ionic chlorine, bromine and iodine pass rapidly across the cell membrane in vitro and that equilibrium is rapidly established. They observed that in the case of iodine the distribution in cells and plasma is about equal. Salter (1940) had previously reported the erythrocyte to contain approximately 50% of the blood iodine. Utilizing I^{131} as a tracer, Scott, et al (1951) studied the effect of various levels of thyroid function on the relative amounts of iodine present in the cells and plasma. They found that the initial cell plasma ratio was the same in hypothyroid, euthyroid, and hyperthyroid patients, but that the ratio dropped as the inorganic I^{131} was bound to protein in the thyroid. The drop in the cell plasma ratio was caused by the impermeability of the cells to the larger protein-combined molecules. The rate of drop of the cell plasma ratio is interpreted as an expression of thyroid activity.

Boatman and Moses (1951 a) determined only a slight rise of I^{131} in the plasma twenty-four hours after an intraperitoneal injection, the cell plasma ratio being quite constant over a twenty-four hour period.

MATERIALS AND METHODS

General

Twelve pups were procured at the age of six and one-half weeks. There were two litters of six pups each, one litter being a collie-farm shepherd cross, and the other a shepherd-setter cross, in so far as the owners were able to acertain. One pup in the shepherd-setter litter was a male, the remainder of this litter and all of the other litter were females. The pups were divided at random into four groups, two pups from each litter being placed in a group. Identification, was achieved by tatooing the assigned numbers on the inner surface of the ear flap. The male pup was number 4 in the thiouracil group. The animals were of fairly uniform size and stature at the onset of the experiment (see Figures I and II).

The animals were housed in the central portion of Animal Disease barn No. 2 in individual kennels built especially for this experiment. These kennels were of 2x4 frame construction with chicken wire sides, tops and doors. Shavings were used as bedding material and were changed daily. The room temperature fluctuated between 58° and 68° F. Humidity and odor was controlled by an exhaust fan system. These animals were not allowed out of doors, but were allowed to exercise inside while the kennels were being cleaned.

From the beginning of the experiment until the animals were three months of age they were fed three times daily. The first feeding, at 7 a.m., consisted of canned Ken-L-Ration dog food and fresh skim milk. At noon they were fed skim milk and about 6 p.m. they were given skim milk, canned Ken-L-Ration and Ken-L-Biskit.

From three months of age until the termination of the experiment the dogs were fed a combination of fresh skim milk and Ken-L-Biskit dog food morning and night. The amount of food given each dog was governed by the feeder's experience as to how much the individual would eat. The animals were full-fed as nearly as possible.

Water was placed before the dogs twice daily for a period of about ten minutes. It was found that the quantity consumed when given in this manner was quite small.

As soon as the dogs were procured they were given 1cc. per pound of body weight of anti-canine distemper serum subcutaneously in the cervical region. This was repeated two weeks later.

At three months of age each animal was given 1cc. of Ashe-Lockhart distemper vaccine intradermally in the flank fold. This procedure was repeated ten days later.

The dogs were heavily infested with toxacara caninum at the onset. They were given Vermiplex (Pitman-Moore) in prescribed dosage to relieve this condition. Two weeks later another dose of this compound was given, and thereafter no evidence of intestinal parasites could be found upon microscopic examination of the feces.

A heavy infestation of ctenocephalides caninum necessitated the use of pyrone powder (Jen-Sal) containing 10% D.D.T. This powder was applied four times at five day intervals, and following that only when it was thought necessary.

Thyroidectomy

Thyroidectomy was performed on four of the puppies seven days after the initial data were taken. The animals were anesthetized with Halatol (Jen-Sal) given intravenously in the cephalic vein. They were clipped over the ventral portion of the anterior cervical region, and this area scrubbed with liquid germicidal detergent.

An incision was made through the skin on the mid-line extending from the level of the cricoid cartilage distally for a distance of 4 cm. The sterno-hyoid muscles were separated for the same length and this region of the trachea was bared. The thyroid glands were disected free of fatty tissue. The external parathyroid, lying on the antero-lateral surface of the thyroid was located in all but one case. This was dissected away from the surface of the thyroid gland taking care to preserve the small branches of the anterior thyroid vessels supplying it. The anterior thyroid vessels were then ligated distal to the point where the parathyroid branches left it.

The lobe of the thyroid which was disected free first was left in position until that of the opposite side was free. They were then removed simultaneously taking the thin isthmus of facia which crosses the ventral surface of the trachea with them.

The muscle separation was then closed with interrupted sutures of cotton. The skin incision was closed in the same manner.

Recovery from the operation was uneventful and the sutures were removed five days later with good healing evident.

Seven days following the operation one of the dogs showed symptoms of tetany when being handled. Symptoms were relieved with the intravenous injection of 5 cc of a 10% solution of calcium gluconate twice daily. The animal died two days later. This dog was the one in which we had difficulty locating the parathyroids. None of the other individuals of the group showed any deviation from normal.

Thiouracil Administration

The administration of powdered 2-thiouracil* was started in four of the remaining eight animals on the day following thyroidectomy of the four dogs previously mentioned. It was given by individual dosage by means of gelatin capsules. The dogs were given the drug at approximately 7 a.m. and 6 p.m. daily, at least ten minutes before they were fed. The dosage given was approximate but an effort was made to administer 25 to 40 mg per kg twice daily. This was accomplished by weighing an empty capsule first, then filling it in a standard manner and reweighing it. By subtracting the two values we were able to acertain the amount of 2-thiouracil each capsule size would hold. Rather than weighing individual capsules, the one weighed initially was used as a standard by which to pack the capsules used in the experiment. The animals were started on a dosage of 140 mg of 2-thiouracil twice daily and as the body weight of the individuals increased so that the level given reached the lower range it was again adjusted to the point where the animal was receiving close to 40 mg/kg twice daily.

Body Weights

The dogs were weighed before the evening feeding at seven day intervals during the experiment on a spring type dairy scale. It was found that the animals were too active to be weighed in the basket with which this scale was equipped, so a rope sling was fashioned. A rope loop, approximately three feet in diameter was placed on the floor between the front and rear legs with the dog in standing position. The anterior part of this loop was drawn between the forelimbs and the loop thus formed drawn over the head so that it rested just anterior to the shoulders. The edges of the original loop were then picked up on either side of the dog and brought together over the back. It was found that the dog could be elevated to the scale hook in a harness of this type with very little discomfort and a minimum of struggling. As a result, the weight could be easily read to the nearest quarter-pound with some degree of accuracy.

Tibial Measurements

Radiographs were taken of the left tibia in lateral position at four to six-week intervals during the experiment. The machine used was a 10 milliampere General Electric portable. The cassettes were screen-type bakelite without grid inserts. Kodak Blue Brand medical x-ray film was used.

The animal was placed in lateral recumbency with the left leg in contact with the x-ray cassette. The right leg was held forward and outward to avoid interference. The tibia was aligned to be directly in the path of the x-rays. Relaxation was attained by holding the animal in this position for a few moments before the radiograph was taken. Exposures were standardized at 10 milliamperes and 50 kilovolt potential for .25 second at a distance of 26 inches in all cases. The films were processed in the conventional method.

Measurements were made from the original radiographs of the overall length of the tibia, width of the tibial diaphysis at midshaft, width at the distal epiphyseal fusion point, and the proximal and distal fusion points of the tibial tubercle. A transparent mm scale was used in these measurements.

In order to facilitate printing, the films were increased slightly from their original size in a uniform manner so that differences would still be apparent.

Dentition

Examination of the mouth of each animal was performed weekly, noting primarily the appearance time of the secondary teeth.

Body Temperatures

Rectal temperatures were taken weekly with the animals in a post-absorptive state. A standardized Fahrenheit rectal thermometer was used. The thermometer was left in place for two minutes before being read.

Since the animals were easily excited when anyone was in the room, it was decided to start with a different dog each time the temperatures were taken. It was thought that this might compensate to some degree for the temperature rise associated with excitement.

Pulse Rates

Pulse rates were taken weekly on the animals from the fifth to the thirteenth week of the experiment. The pulse was taken directly over the heart by palpation. Counts were taken for a full minute and recorded in this manner. Pulse rates were taken in the same order as the body temperatures.

Food Intake

A rough estimate of the food intake was made by measuring the amount of food fed in a pint measure and subtracting the amount which was left. The value thus derived was recorded in pounds.

Blood Examination

During the last week of the experiment 5 cc of blood was drawn from the cephalic vein of each animal. This was placed immediately in a vial containing sodium oxalate. Data were recorded for the following:

1) The red blood cell count, using the standard haemocytometer method.

2) The hemoglobin was estimated with the use of the Sahli hemometer. Results were read in grams.

3) The white blood cell counts, using the standard haemocytometer methods.

4) Cell volume was estimated by the method of Wintrobe.

5) Sedimentation time was determined by Westergren's method.

6) Differential Counts. Blood smears were stained with Wright's stain and 100 white cells counted and classified in each case.

The methods used in this part of the work were described by Todd and Sanford (1948).

I^{131} Uptake

Five-tenths cc of a stock solution containing 1500 microcuries per cc of I^{131} as sodium iodide was diluted with 40 cc of distilled water to give a solution strength of approximately 20 microcuries per cc.

Each dog was given .1 cc per pound of body weight of this solution intravenously via the cephalic vein. A separate needle was used to withdraw the radioactive material from the storage vial. After the material was injected into the vein, blood was drawn into the syringe two or three times and reinjected into the vein to avoid deposition of the radioactive material around the site of puncture.

The animal was then removed to an adjacent room where background counts were taken. Counts were then taken over the thyroid and over the medial aspect of the tibial region. The total time elapsed between the time of injection and the first series of counts was five minutes.

Subsequent counts were taken in this manner at 12, 24, 48, 72 and 170 hours after the injection.

A Tracerlab portable laboratory monitor was used for making the counts.

<u>Cell Plasma Ratios of I^{131}</u>

Blood samples were drawn from the jugular vein 5 minutes, 12, 24, 48 and 72 hours after the injection of I^{131} described above. Care was taken to avoid the region of the thyroid. The venipuncture was made as far caudally as possible. A sample of 10cc of blood from each animal was placed in tubes containing .5 cc of 30% sodium citrate solution and mixed gently.

Separation of the cells and plasma and subsequent counting was performed by the method described by Scott, et al (1951).

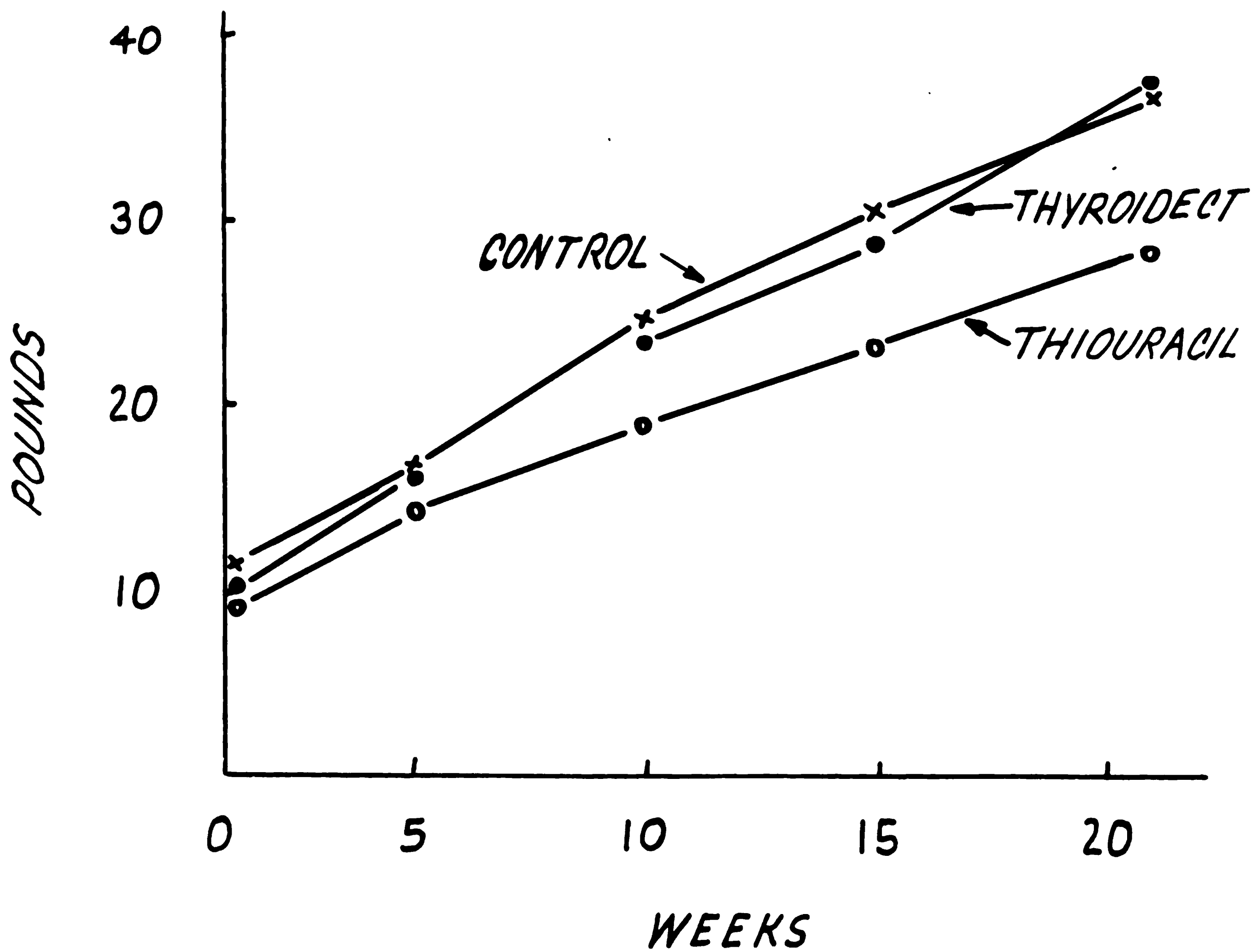
RESULTS

Body Weight

Appendix tables I, IA and IB show the overall tabulation of body weights during the experiment. Note that in appendix table II in which body weight averages are given that the thiouracil group averaged consistently less than the other two groups, and that the thyroidectomized and control groups were quite consistently alike, within experimental error.

Figure I on the following page points out that the differences in weight gain between the thiouracil group and the two remaining groups increase as the experimental period increases. At the onset of the experiment there was approximately one pound difference in the groups and at the end of the experiment the thiouracil group averaged about eight pounds less than the others.

These differences did not prove to be statistically significant when checked by means of analysis of covariance, because of the failure of dog number 5 to gain weight in relation to the other members of the group.



BODY WEIGHTS Fig. I

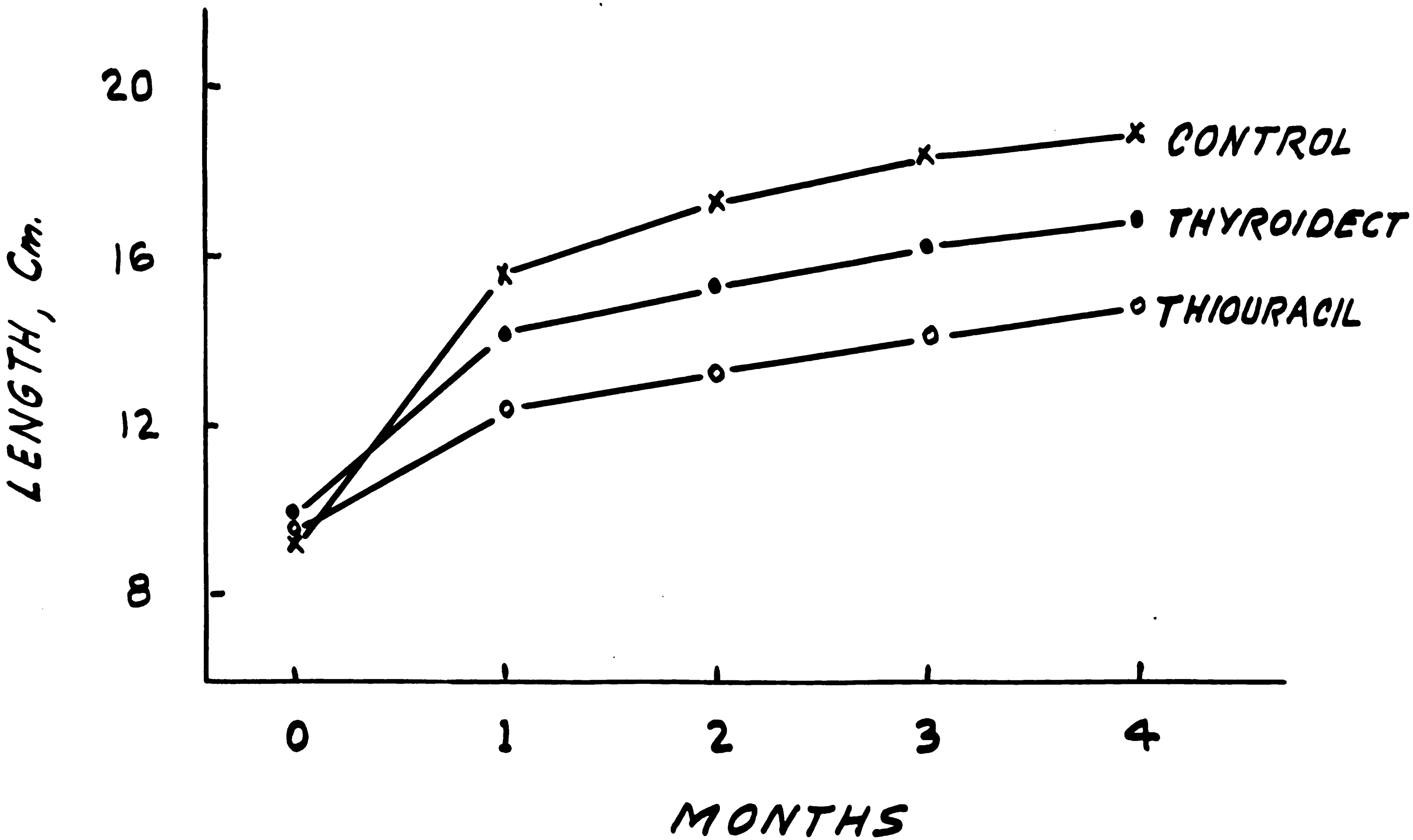
Tibial Measurements

The tibias of the control group of dogs grew more rapidly and attained greater final length during the course of the experiment than the thiouracil-treated or thyroidectomized group as shown by figure II. The thyroidectomized animals grew faster than the thiouracil group as measured by growth in length of the tibia. Complete data on tibial length measurements and group averages are given in appendix tables III and IV. These differences were highly significant when subjected to an analysis of covariance.

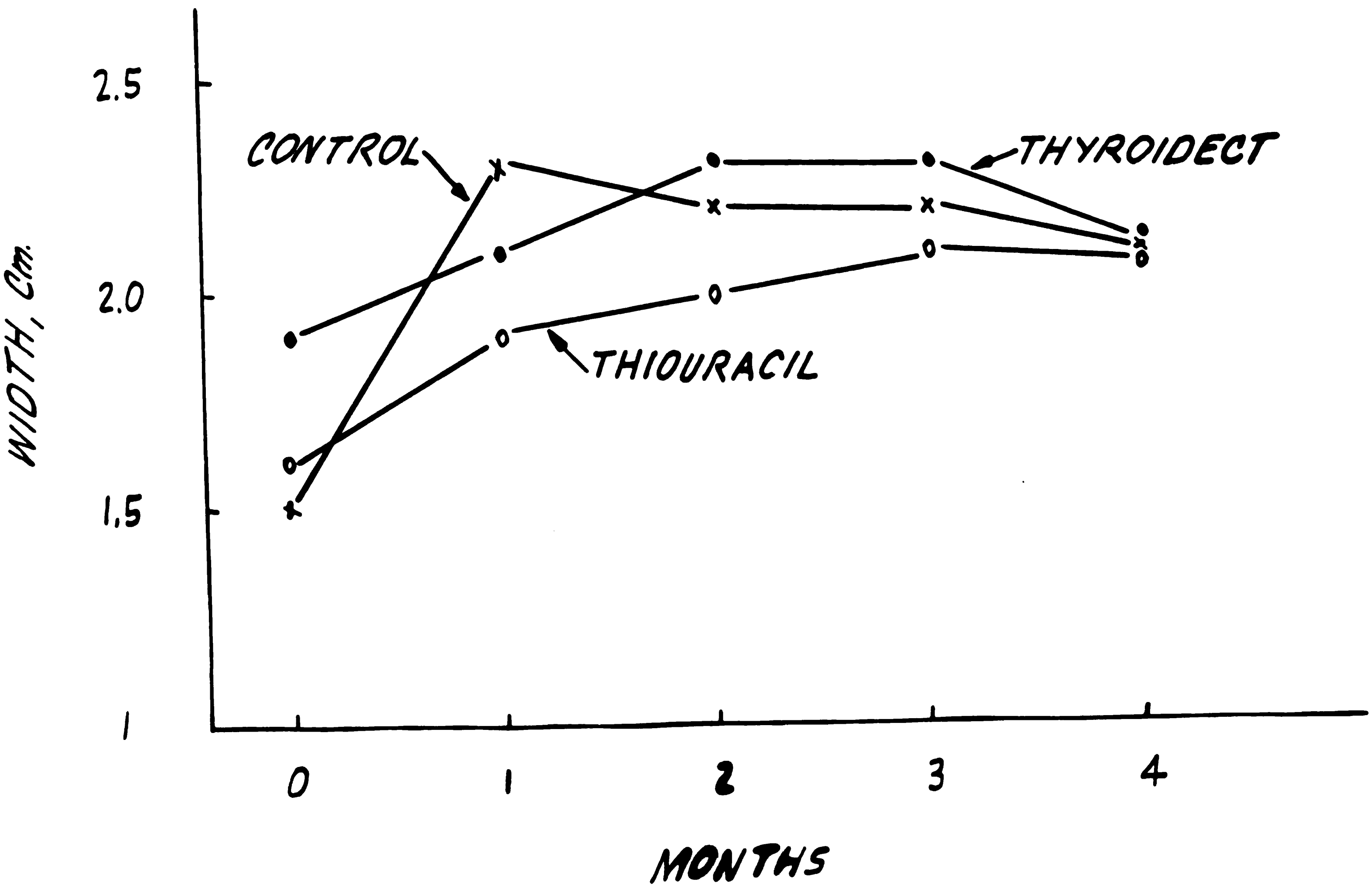
Measurements of the distal epiphysis of the tibia show what is apparently a lag in the development of this bone in the thiouracil group. The dogs of the control group showed the greatest mean width of tibial epiphysis at the second month, and the thyroidectomized group at the third and fourth months, whereas the thiouracil-treated group had apparently not reached its greatest mean width at the time of the last radiograph. This is shown by figure III. The specific measurements and averages are shown in tables V and VI in the appendix. The differences are not statistically significant.

The tibial diaphysis ultimately grew wider in the control group than in the other groups as can be seen in tables VII and VIII of the appendix. These differences were slight but approached significance when subjected to analysis of covariance.

In measuring the proximal and distal unfused areas of the tibial tubercle it was noted that proximal fusion which seems to take place first was complete about two months earlier in the control group than in either the thiouracil or thyroidectomized groups. Distal fusion was also advanced in the control group. This slowing of fusion was more noticeable in the thiouracil group than in the thyroidectomized group. See table A. page 38, and figures IX to XIX in the appendix.



TIBIAL LENGTHS Fig. II



WIDTH OF TIBIAL EPIPHYSIS Fig. III

TABLE A

FUSION OF TIBIAL TUBERCLE

MEASUREMENT OF PROXIMAL AND DISTAL GAPS (MM)

Dog No.	12/12		1/20		2/20		3/20		4/10	
	P*	D*	P	D	P	D	P	D	P	D
I. Thiouracil										
2	5	3	5	5	1	6	1	6	PF*	6
3	5	3	2	6	1	6	.5	7	PF	6
4	6	5	1	6	.5	5	.5	4	F*	4
5	7	4	2	2	2	2	.5	4	.5	3
II. Control										
6	6	4	.5	6	F	6	F	5	F	3.5
7	6	4	.5	6	F	7	F	6	F	1
8	7	4	1	5	F	4	F	4	F	4
9	6	6	1	6	F	4	F	3	F	2
III. Thyroidectomized										
10	6	6	2	12	1	12	5	12	F	4
11	7	5	2	6	.5	6	.5	5	F	4
12	7	7	5	7	2	7	.5	7	F	5

*PF Partial Fusion
*F Ossification complete

*P Proximal - unossified area
*D Distal - unossified area

Dentition

In all but one case eruption of secondary teeth started earlier in the control group than in the thyroidectomized and thiouracil-treated groups. The time at which secondary dentition was complete was essentially the same in all groups.

It should be mentioned that retained primary canine teeth were noted in two cases in the thiouracil group, but in none of the control or thyroidectomized pups.

A tabulation of the eruption times of the secondary teeth is given in tables IX, X and XI of the appendix.

Body Temperatures

After the first three temperature recordings were taken, in which cases the body temperatures averaged about the same in all three groups, the controls invariably had a higher mean body temperature than the other two groups, (Table B). These differences approached significance in several instances, but the F value exceeded significance on only three occasions. This was on 1/23, 2/27 and 3/6. In no instance was the difference highly significant.

TABLE B

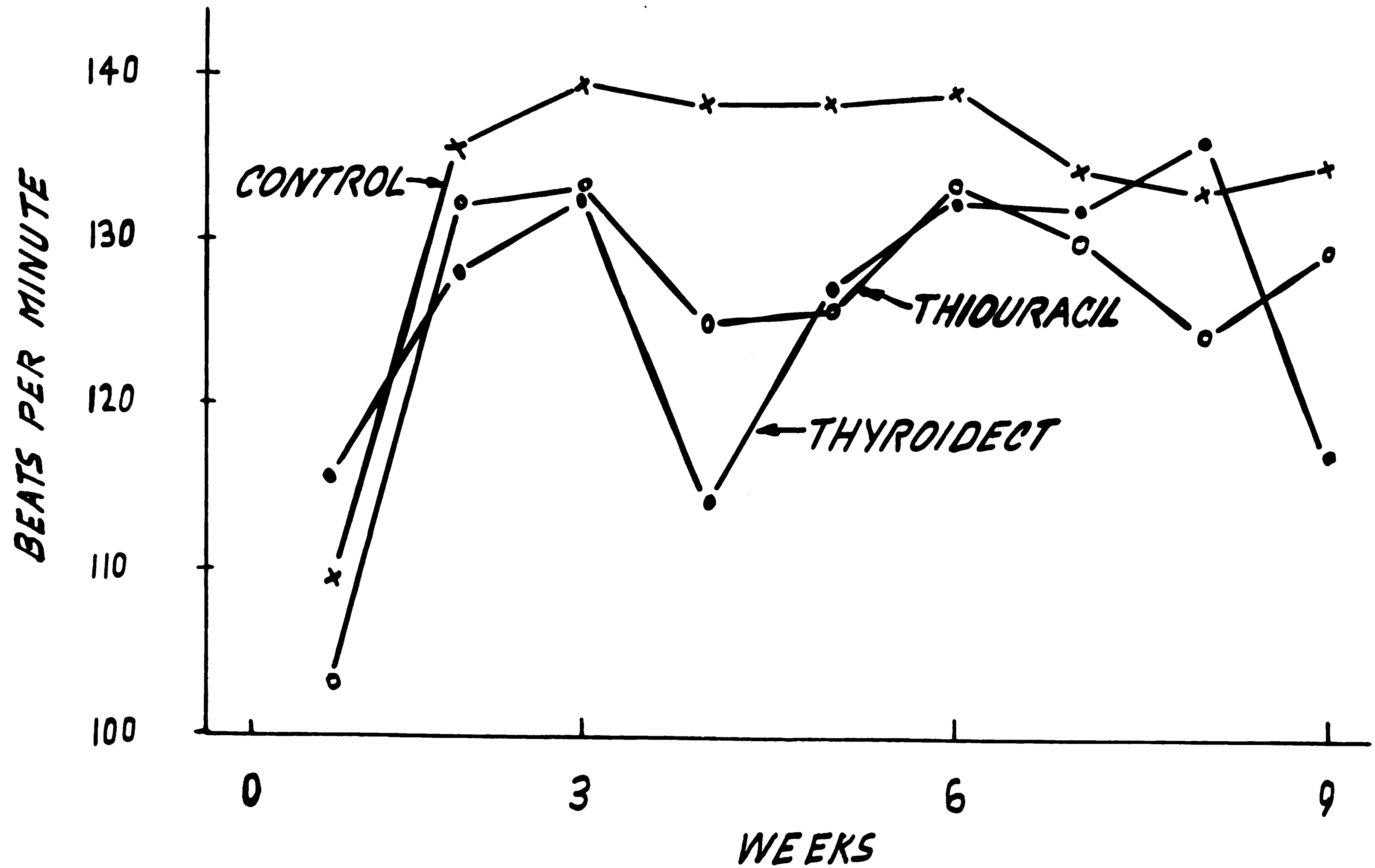
BODY TEMPERATURES - GROUP AVERAGES

Date	Thiouracil	Control	Thyroidectomized
12/12	101.7±.2	101.8±.2	101.8±.2
12/19	101.9±.1	101.8±.1	102.1±.2
1/2	102.1±.2	101.9±.2	101.7±.2
1/9	102.1±.2	102.3±.2	101.9±.2
1/16	102.3±.2	102.3±.2	101.9±.2
1/23	102.1±.2	103.2±.2	102.0±.3
1/30	102.4±.2	103.0±.2	102.2±.2
2/6	102.3±.3	103.3±.3	102.2±.3
2/13	102.4±.3	103.0±.3	101.9±.3
2/20	102.4±.2	103.1±.2	102.1±.3
2/27	102.4±.3	103.4±.3	101.9±.3
3/6	102.5±.2	103.1±.2	102.0±.2
3/13	102.9±.5	103.5±.5	102.5±.6
3/20	102.5±.2	102.8±.2	101.9±.3
3/27	102.7±.3	103.7±.3	102.5±.4
4/3	102.8±.3	103.3±.3	102.3±.3
4/10	102.5±.3	103.3±.3	102.2±.3

± standard error

Pulse Rates

The average pulse rates are presented in table XIV of the appendix. Complete data appear in table XIII. The results are inconsistent and in no case are the differences significant. It is of interest to note that the pulse rate of the control group was in most instances higher than the thiouracil-treated or thyroidectomized groups, much in the manner of the body temperature. Figure IV on the next page shows this relationship.

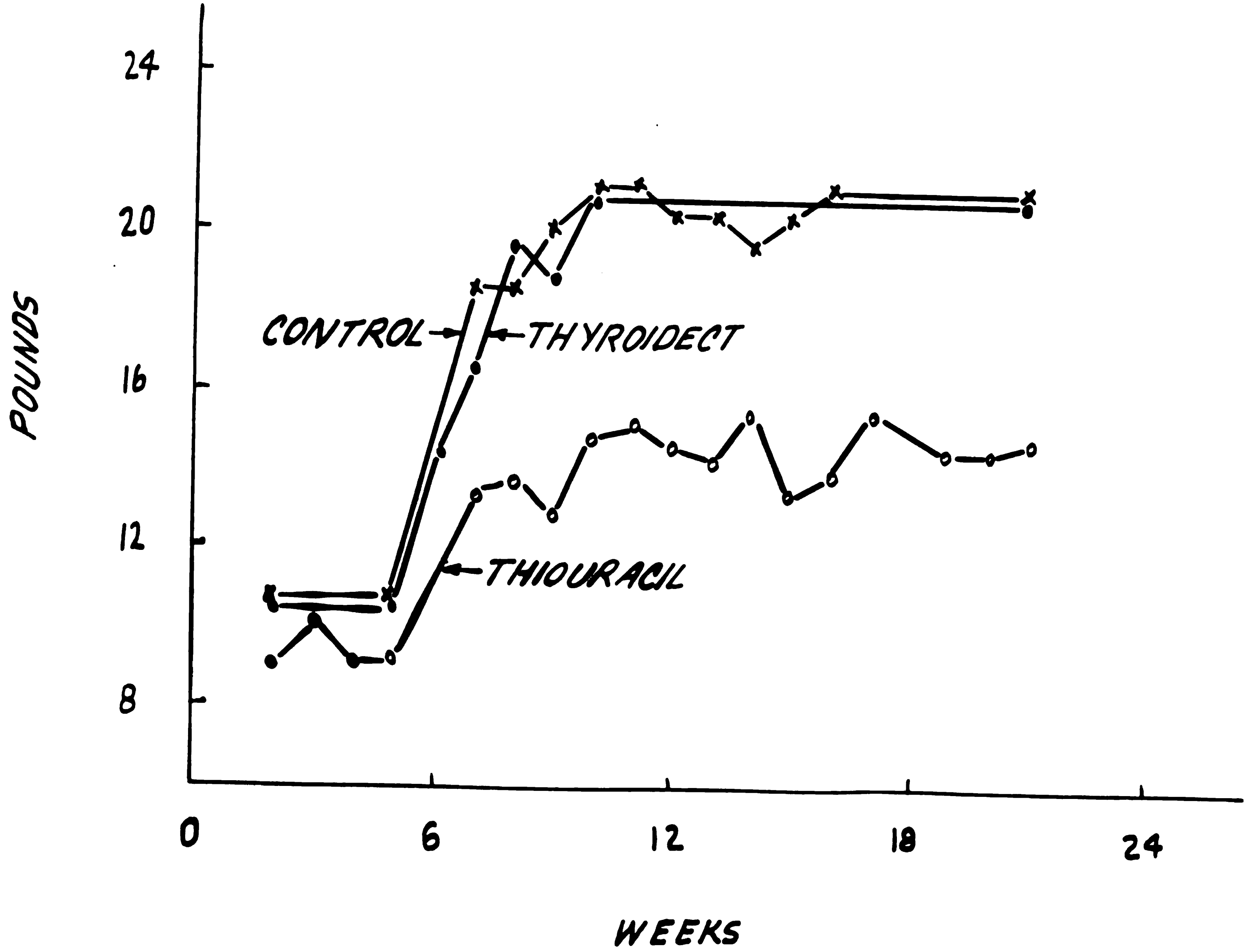


PULSE RATES Fig. IV

Food Intake

Complete data on food intake are shown in table XV in the appendix. The thyroidectomized and control groups consumed food at about the same rate throughout the experiment. The thiouracil-treated group as a whole consumed considerably less food and their appetites were very erratic. Even when the food consumption in this group approached that of the other two groups, it was noted that these animals seemed to relish food to a lesser extent and frequently ate all the food given if it was left in the kennel overnight. The relationship of these approximate figures can be seen in figure V on the next page.

It should be noted that the control group were much more active than the thyroidectomized or thiouracil groups. The latter two groups were quite listless and showed a tendency to react more slowly to handling than did the controls.



FOOD INTAKE Fig. V

Blood Examination

The red blood cell counts of the thiouracil-treated group of dogs averaged significantly less than those of either the control or thyroidectomized groups. The thyroidectomized group had significantly lower red blood cell counts than the control group of dogs.

In hemoglobin, cell volume, and sedimentation time determinations the thiouracil-treated group consistently averaged significantly less than the other groups. There were no significant differences in these determinations between the control and thyroidectomized groups.

The total and differential white blood cell counts showed no significant differences.

These data are presented in their entirety in appendix table XVII, and their averages in table C on the following page.

TABLE C

BLOOD EXAMINATION - GROUP AVERAGES

Group	R.B.C.	W.B.C.	Hb. (Gm.)	Cell Volume	Sedimentation Time 30 min.	60 min.
Thiouracil Dogs 2,3,4,5	4,240,000±370,000	12,790±1,245	12,8±.35	27.1±1.6	2±.44	6.4±.15
Control Dogs 6,7,8,9	6,865,000±370,000	11,700±1,245	18.1±.35	45.6±1.6	.25±.44	.75±.15
Thyroidectomized Dogs 10,11,12	5,820,000±427,000	11,780±1,439	17.3±.4	40.0±1.9	.33±.51	.83±.17

Differential Counts - %

Group	Neutrophils Seg.	Non-Seg.	Lymph	Mono	Eosin	Baso
Thiouracil Dogs 2,3,4,5	40±14.5	17±3.3	39±6.2	2	2	1
Control Dogs 6,7,8,9	40±14.5	32±3.3	26±6.2	2	1	0
Thyroidectomized Dogs 10,11,12	40±16.7	28±3.8	28±7.8	1	2	1

± standard error

I^{131} Uptake

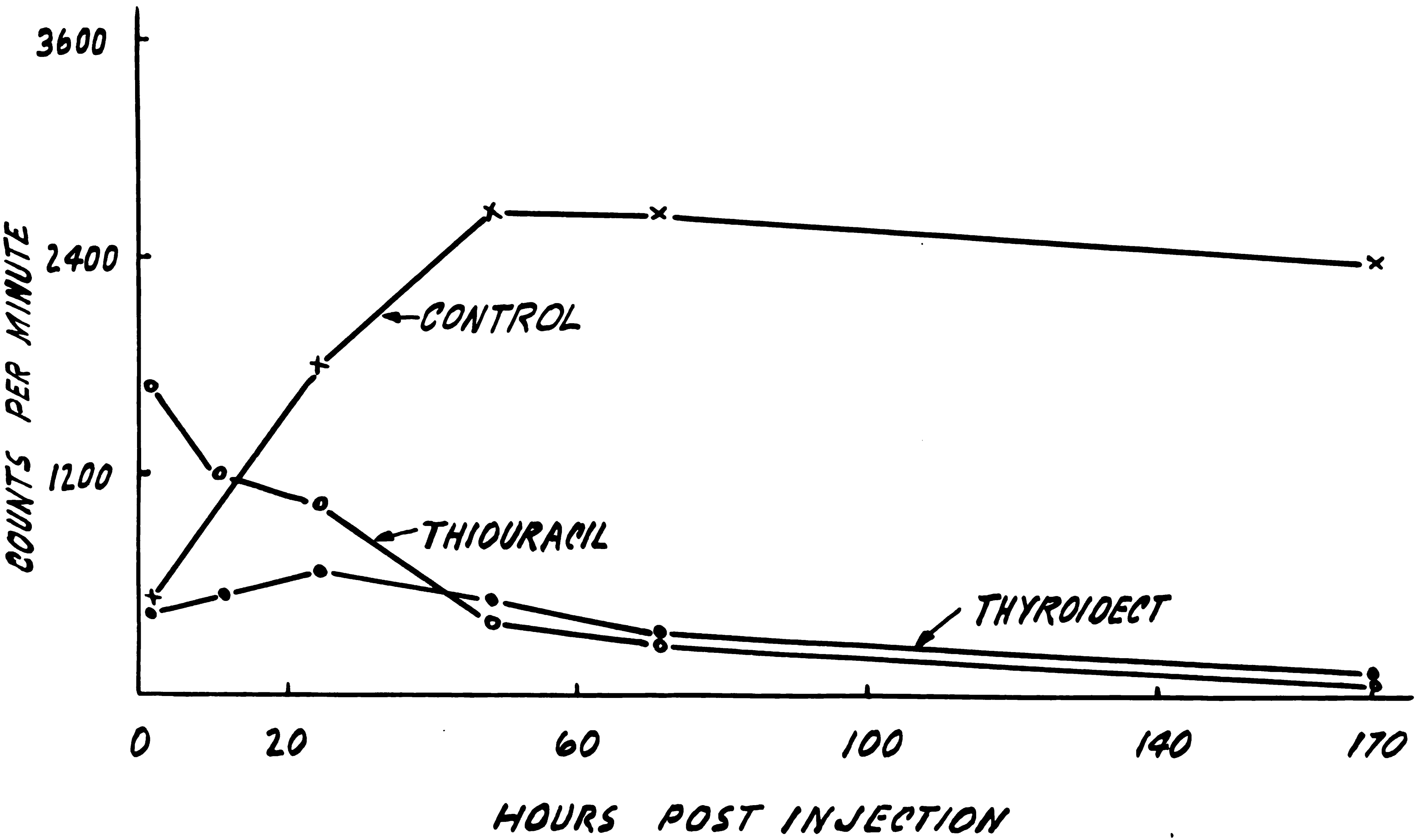
In considering the uptake of radioactive I^{131} as recorded by counting over the thyroid region, it was found that the thiouracil-treated animals took up the material very rapidly, but returned approximately to the level of the controls at 48 hours post-injection. The initial level exhibited by the thyroidectomized group, taken at 5 minutes post-injection was approximately the same as the controls, but the uptake by the thyroids of the controls increased steadily until the peak was reached at 72 hours. A considerably slower uptake occurred than in the case of the thiouracil-treated animals.

The graphic representation is shown in figure VI.

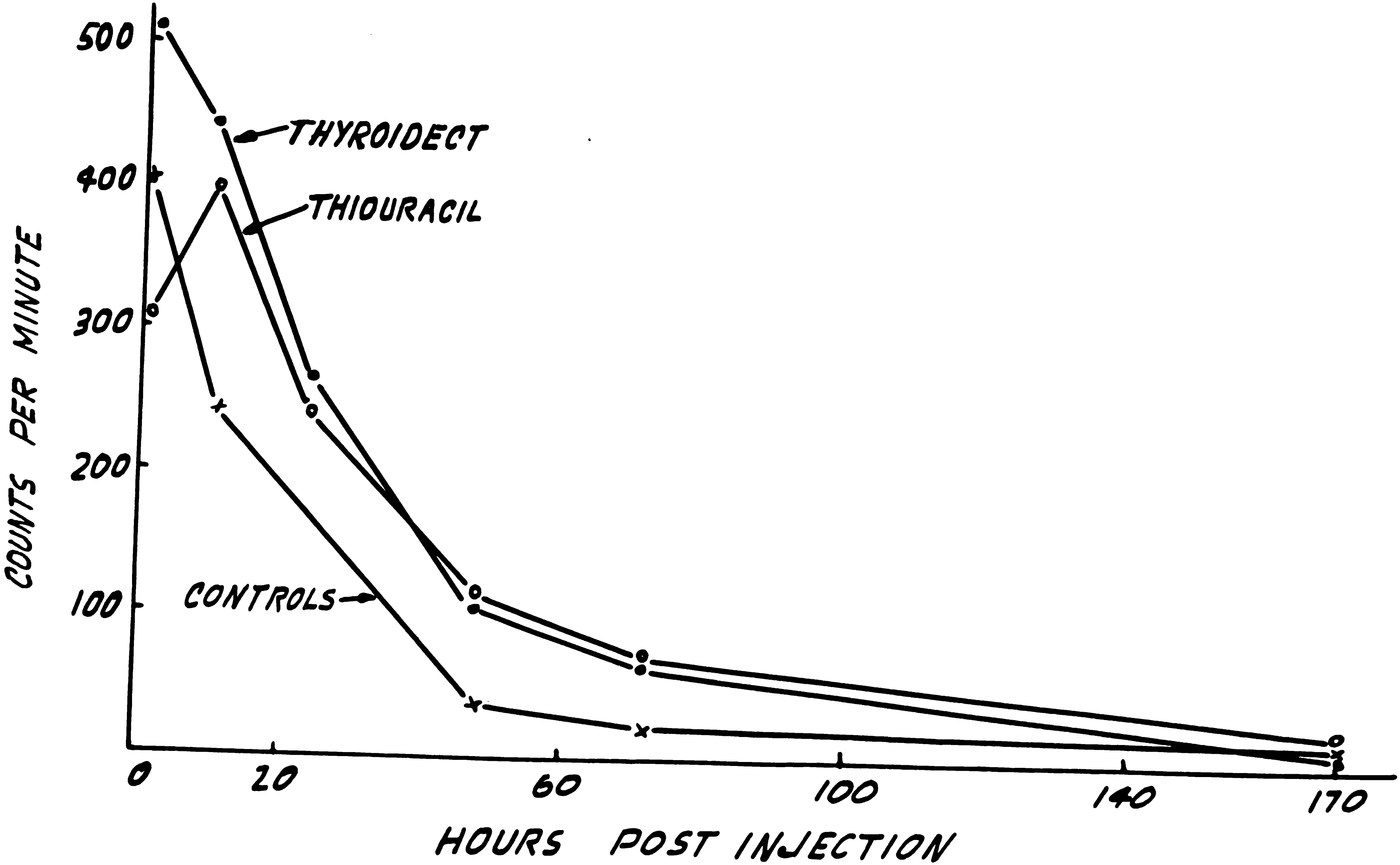
The amount of radioactivity as recorded over the medial aspect of the tibial region shows a reciprocal of the thyroid uptake on a lesser scale. The control group showed an initial higher level which gradually decreased until only a very small amount remained at 170 hours. The thiouracil-treated group showed lower levels until 48 hours at which time it became essentially the same as the control group. The thyroidectomized group showed constantly lower levels over the extremities until about 140 hours at which time it became the same as the control group.

These results are shown in figure VII.

Complete data and averages on thyroid and extremity counts are given in appendix tables XVII and XVIII.



THYROID COUNTS I^{131} Fig. VI

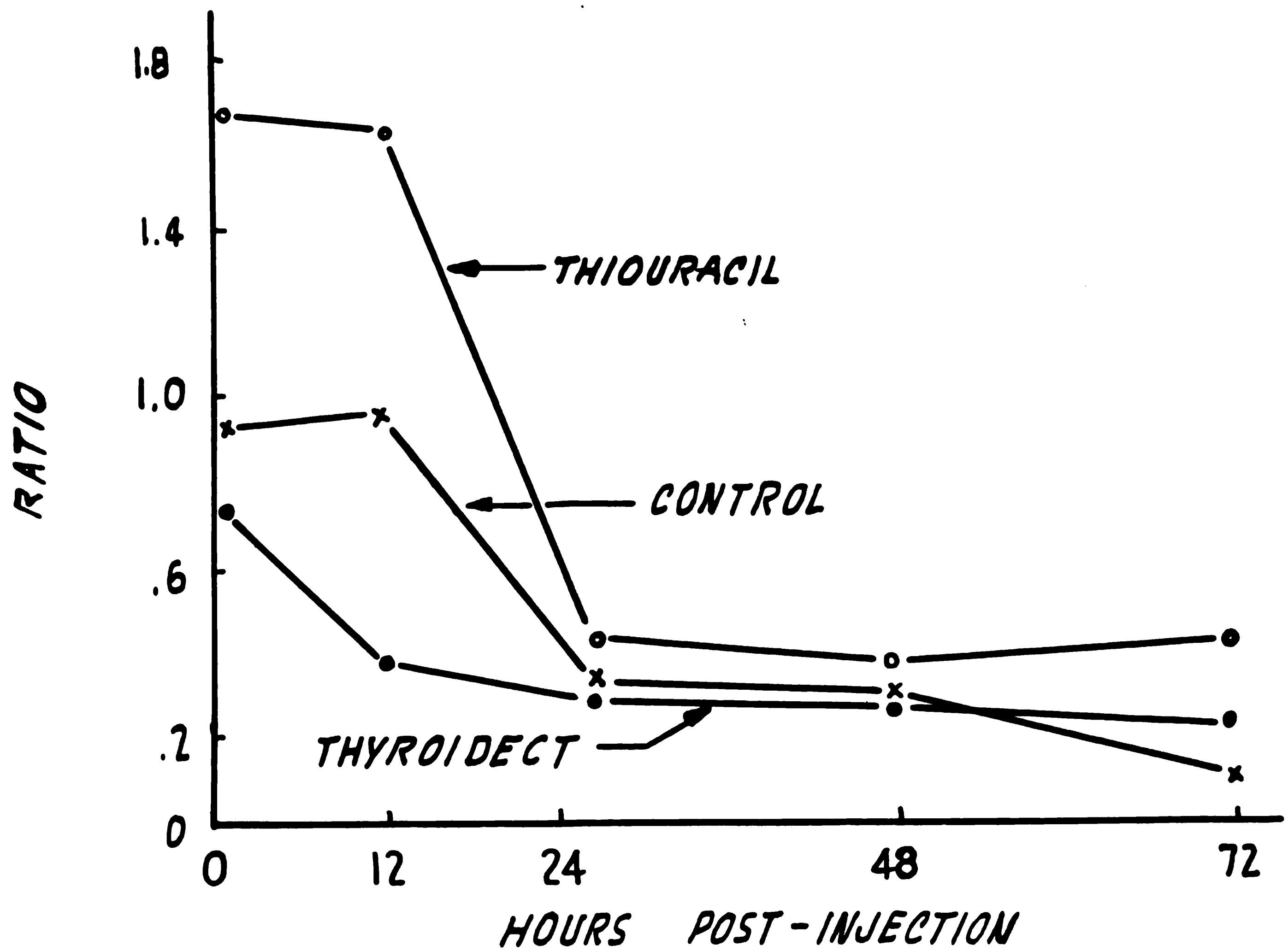


EXTREMITY COUNTS I^{131} Fig. VII

Cell Plasma Ratios, I^{131}

Initial and 12 hour cell plasma ratios were quite variable, the thiouracil-treated group showing higher and the thyroidectomized group showing significantly lower levels than the controls. There were no significant differences in the ratios exhibited by the groups at 24 or 48 hours post-injection, but at 72 hours there was a lower ratio exhibited by the control group than the other groups. This value was significantly lower than that of the thiouracil-treated group, and approached significance when compared to the thyroidectomized group.

The results are shown in figure VIII on the following page and complete data in table XIX and XX in the appendix.



CELL/PLASMA RATIOS Fig. VIII

DISCUSSION

From the previous experiments by Danowski et al (1946), Mayer (1947), and Glock (1949) one would assume that the administration of thiouracil to dogs does not produce effects similar to those of thyroidectomy as previously described by Dye and Maugham (1929), and Binswanger (1936). In this experiment similar effects were noted in thyroidectomized and thiouracil groups on the body weight, skeletal growth, dental eruption, blood picture, and cell plasma ratios of I^{131}.

It seems desirable to discuss body weight and skeletal measurements together as they are closely associated in the growth of the animal.

Dye and Maugham (1929) described distinct inhibition of weight gain and skeletal length in young dogs following thyroidectomy. Binswanger (1936) reported similar results. Thiouracil-treated dogs did not respond in this manner as was reported by Mayer (1947) and Glock (1949).

No significant weight differences were noted among the groups in the present experiment, but, although the weight gains were fairly consistent in all groups, there was definite inhibition of tibial growth in the animals made hypothyroid by thiouracil administration or thyroidectomy.

One must theorize to some extent to derive a reason for the differences between the results reported herein, and the results of previous work on the influence of thiouracil administration on growing dogs. There has been no published data on the amount of thiouracil and the frequency of administration necessary to maintain stasis of thyroxine production in the dog. Williams (1944) reported rapid absorption after oral administration of thiouracil to man, maximal blood levels being reached thirty minutes to two hours after administration. Paschkis, et al (1945) reported very rapid excretion in the urine, with excretion almost completed eighteen hours after the administration. Ely, et al (1948) reported that peak levels are not reached in the blood of ruminants until four to eight hours after a single dose of thiouracil, and that elimination is complete at twenty-four hours. They concluded that in order to gain maximal effects thiouracil should be given at least every twelve hours. It would seem that this dosage schedule might have to be lowered in the case of non-ruminants as indicated by the previous work in human beings.

Mayer (1947) administered thiouracil to his dogs twice daily, at 8 a.m. and 3 p.m., on weekdays, once on Saturday and the animals received none at all on Sunday. In another group of dogs on a thiouracil trial, Glock (1949), administered thiouracil every twelve hours for the first three weeks and thence only once daily for the remainder of the experiment. It would seem that these dosage schedules would have left adequate gaps in the thiouracil block which could have allowed the thyroid to resume function and to some extent satisfy the demands of the animal.

With the deletion of dog number 5 in the thiouracil group which did not conform to his group mates in growth or weight gain, there is little or no difference between the thiouracil-treated and thyroidectomized groups in the experiment described here. Both groups show essentially the same relation to the control group having gained about as much in weight, but lagging significantly in skeletal growth.

The tibial diaphysis width of the thiouracil-treated and thyroidectomized groups averaged only slightly less than in the controls. The tibial length differences were much greater. This confirms the data reported by Dye and Maugham (1929) who found that length, but not width of bones was adversely affected by thyroidectomy.

The slower fusion of the tibial tubercle in the thiouracil-treated and thyroidectomized groups resembles the radiographic findings reported in hypothyroidism of children by Schaefer and Purcell (1941).

Dental eruption dates in these animals conform well with the findings in dogs by Binswanger (1936) who stated that in thyroidectomized individuals secondary dentition occurred from one to two weeks later than in controls. The thiouracil-treated and the thyroidectomized animals in this experiment followed a similar course. Liddell (1925) reported a like condition in thyroidectomized sheep. No effect on dentition was noted in young dogs following thyroidectomy by Dye and Maugham (1929).

The reason why dentition was complete in all groups of this experiment at the same time despite the retarded eruption in the hypothyroid groups is not understood.

Although the body temperature was not significantly affected by thiouracil administration or thyroidectomy it was found that the control dogs almost invariably showed a higher mean body temperature. Only slight influence on body temperature following thyroidectomy in dogs has been reported in previous experiments by Binswanger (1936) and Borgman (1949). It may be possible in this experiment to attribute the slightly higher temperatures in the control animals to the fact that they were more easily excited and reacted with much more vigor to handling than did the hypothyroid individuals.

Binswanger (1936) observed a decrease in the pulse rate of thyroidectomized dogs. A 16% drop in pulse rate was reported by Borgman (1949) after thyroidectomy of adult dogs. Leblond and Hoff (1944) reported a reduction of pulse rate of about 30% in rats fed thiourea over a four months period.

The differences noted in this experiment were not as striking as those previously reported and were not statistically significant. However, the control animals almost invariably showed a higher rate than the hypothyroid animals. It is noteworthy that the thiouracil-treated group and the thyroidectomized group had very similar pulse rates during the course of the experiment.

The food consumption was not influenced in this case by thyroidectomy. Borgman (1949) noted a decrease in food intake following thyroidectomy in adult dogs.

The food intake was distinctly lowered in the thiouracil-treated group. All dogs in the group showed this effect, some to a greater degree than others. Mayer (1947) and Glock (1949) did not report lowered food intake as a result of thiouracil administration. This effect is quite well established in the meat-producing animals (Mixner et al 1946; Andrews et al 1947). In these cases the lower food consumption was associated with increased weight gain, whereas weight gains were not significantly effected in the present experiment.

Although the thiouracil-treated and thyroidectomized animals in this study showed distinct listlessness and lack of vigor, abnormalities of the skin and hair coat and edema of the neck and sternal regions as observed by Goldberg and Chaikoff (1952) in adult dogs was not seen. This might be explained by the fact that these animals were on experiment for a comparatively short period of time.

Following thyroidectomy of dogs by the use of I^{131}, Goldberg and Chaikoff (1952) reported a 20 to 30% drop in the red blood cell counts. Kunde, et al (1932) reported macrocytic anemia and decreased hemoglobin and cell volume in thyroidectomized rabbits. A mild anemia was reported by Leathem (1945) in rats following thiouracil administration.

The dogs of both the thiouracil-treated and thyroidectomized groups showed a significant decrease in red blood cell count as compared to the control group in this case. This is in contrast to the results reported by Mayer (1949) who found no changes from normal in the blood picture of thiouracil-treated dogs.

The hemoglobin and cell volume were significantly lower in the thiouracil-treated group than in the control group. The thyroidectomized animals showed lower values of hemoglobin and cell volume than the controls, but these results only approached significance.

There were no apparent effects on the leucocytic elements of the blood due to thiouracil administration or thyroidectomy in this experiment. This is in contrast to reports by Kahn and Stock (1944), and Gargill and Lesses (1945) of cases in human beings in which agranulocytosis was observed following thiouracil therapy of thyrotoxicosis. Williams, et al (1944) in a compilation of cases treated with thiouracil stated that only 1.2% showed agranulocytosis. This figure is much less than the 20% reported by Fishberg and Vorzimer (1945).

The sedimentation rate of the blood of the thiouracil-treated group was significantly increased in relation to the thyroidectomized and control groups. This effect has not been previously reported.

It was found by Franklin, et al (1944) that the administration of thiouracil did not prevent the uptake of iodine by the thyroid gland. Stanley and Astwood (1947) showed that the thyroid of thiourea-treated patients took up radioiodine very rapidly but did not retain a plateau for over 36 hours, while the controls gained a plateau somewhat more slowly but retained it for a much longer period of time.

The determination of the uptake of radioiodine was performed primarily to give some indication as to the completeness of thyroidectomy. The results were as expected and conform quite well with the previously cited work. The thyroidectomized animals took up very little of the injected dose. The thyroids of the thiouracil-treated group took up the radioiodine very rapidly and the level was apparently beginning to drop at the time the 5 minute counts were taken. The level became approximately the same as that of the thyroidectomized group between 24 and 48 hours after the injection. The control animals took up the radioiodine more slowly, the plateau being reached between 48 and 72 hours post-injection and showed only a slight depression of this level at 170 hours.

The extremity levels were the approximate reciprocal of the thyroid levels. As the thyroid took up the radioiodine, the extremity levels decreased, and as release took place the extremity levels increased relatively.

As stated by Scott et al (1951) the cell plasma ratio after an intravenous injection of I^{131} may be used as an index of thyroid activity. They found that the initial cell plasma ratio was the same in hypothyroid, euthyroid and hyperthyroid patients, but that the ratio dropped as the inorganic I^{131} was bound to protein by the thyroid.

The results in this part of the experiment showed much variability among the groups during the first 24 hours. At 24 hours post-injection the cell plasma ratio had become essentially the same in all groups. The reason for this initial variability is not clearly understood and has not been reported previously. There was a significant decrease in the cell plasma ratio of the control group between 48 and 72 hours after the injection of radioiodine. It may be worthy of note that this change did not occur until about the same time as the plateau was reached in the thyroid uptake of I^{131}.

Boatman and Moses (1951) noted only a slight decrease in the cell plasma ratio of rats 24 hours after an intraperitoneal injection of I^{131}. In view of these findings, one might assume that a longer waiting period might be advisable after the injection of radioiodine if the cell plasma ratio is to be used as an index of thyroid activity.

SUMMARY

The comparative effects of thiouracil administration and thyroidectomy were studied in young, growing dogs.

Thyroidectomy or thiouracil administration did not significantly affect weight gain of the animals as compared to controls, but skeletal growth was significantly inhibited by both means of inducing hypothyroidism.

The width of the tibial diaphysis was only slightly decreased in thyroidectomized and thiouracil treated animals.

The fusion of the tibial tubercle occurred more than a month earlier in the controls than in the hypothyroid animals.

Control animals were one to four weeks earlier in dental eruption time than thyroidectomized and thiouracil-treated animals of the same age, but dentition was complete in all groups at approximately the same time.

Body temperature and pulse rate were not significantly affected by thyroidectomy or thiouracil administration. The control group averaged slightly higher in both cases, probably due to decreased reaction to handling on the part of the hypothyroid individuals.

Thiouracil administration adversely affected food intake, while thyroidectomy did not.

The erythropoietic system was affected adversely by both thyroidectomy and thiouracil administration. The thiouracil-treated group exhibited this effect to a greater degree.

Neither thyroidectomy nor thiouracil administration caused any alteration from normal of the white cell components of the blood.

Thiouracil administration caused a significant increase in the sedimentation time of the blood. This effect was not seen in the thyroidectomized animals.

In I^{131} uptake trials the thyroids of the control animals took up the radioiodine over a period of about 48 hours, then maintained quite constant counts, with a very small loss up to 170 hours after the injection. The thyroids of thiouracil-treated animals picked up I^{131} very rapidly, a plateau probably reached before the 5 minute counts were taken, but returning to the level of the thyroidectomized animals at 48 hours.

Initial and 12 hour cell plasma I^{131} ratios were quite varied among the groups. These ratios were approximately the same at 24 to 48 hours.

The cell plasma I^{131} ratios of the control group fell significantly between 48 and 72 hours after the injection.

The pronounced deviation from the normal of both the iodine turnover and the cell plasma I^{131} ratio of both groups of experimental dogs is considered to be satisfactory evidence that a true condition of hypothyroidism had been established.

CONCLUSIONS

The administration of 25 to 40 mg per kg of 2- thiouracil twice daily to the growing dogs used in this experiment produced effects which were very similar to those of thyroidectomy.

The like effects produced were:

1) No significant effect on body weight gain.

2) Significant inhibition in increase of tibial length while the diaphysis width was only slightly depressed.

3) Inhibition of the fusion of the tibial tubercle.

4) An average two-week delay in the eruption of secondary teeth.

5) No significant alterations of body temperature or pulse rate from normal controls.

6) Anemia of significant proportions.

Thiouracil administration produced some effects which were more pronounced than those of thyroidectomy.

1) The food intake was adversely affected by thiouracil administration, but not by thyroidectomy.

2) The anemia produced was more severe in the thiouracil-treated group.

3) Hemoglobin, cell volume and sedimentation time were significantly lowered by this level of thiouracil administration, but were only slightly affected by thyroidectomy.

The degree of inhibition of the thyroid was as great in thiouracil-treated as in thyroidectomized animals as indicated by the thyroid uptake of I^{131} and the cell plasma I^{131} ratios.

The cell plasma I^{131} ratios were significantly lowered in the control group of animals, but not until at least 48 hours after the intravenous injection of I^{131}.

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APPENDIX

TABLE I

BODY WEIGHTS, POUNDS

Dog No.	Date 12/12	12/19	12/26	1/2	1/9	1/16	1/23	1/30
I. Thiouracil								
2	7.0	7.75	9.25	9.25	8.75	10.75	12.0	12.5
3	9.5	10.0	10.5	11.5	14.5	16.5	18.0	19.25
4	12.0	12.5	13.0	13.75	16.75	19.25	19.5	21.25
5	8.0	8.5	10.0	11.25	12.0	12.5	11.75	12.0
II. Control								
6	9.5	11.0	11.5	13.0	14.75	16.5	17.5	18.75
7	10.5	12.5	13.25	14.25	15.25	16.75	17.75	18.75
8	11.0	11.5	12.25	13.25	15.0	17.0	17.25	18.75
9	9.0	9.0	9.25	11.25	13.5	16.0	16.5	18.0
III. Thyroidectomized								
10	12.25	12.25	12.5	13.25	14.25	16.5	17.5	19.25
11	11.5	11.75	13.25	14.75	15.75	17.0	18.25	20.25
12	10.25	10.5	11.5	12.5	13.75	15.25	16.0	17.25

TABLE IA

BODY WEIGHTS, POUNDS

Dog No.	2/6	2/13	2/20	2/27	3/6	3/13	3/20	3/27
I. Thiouracil								
2	13.75	14.5	15.0	16.0	17.0	17.5	18.0	19.25
3	21.5	23.25	25.0	26.5	27.5	28.75	29.75	30.5
4	23.5	25.0	25.75	25.50	26.5	29.0	29.0	29.25
5	12.5	12.25	11.75	12.0	12.5	12.5	13.0	13.25
II. Control								
6	20.5	22.25	23.5	24.5	26.0	27.5	28.0	29.5
7	20.5	22.0	23.50	24.25	25.5	27.0	27.50	28.75
8	20.25	21.75	23.75	24.25	25.5	26.5	27.0	28.0
9	20.0	21.5	23.0	24.5	25.75	27.5	28.0	29.5
III. Thyroidectomized								
10	21.5	23.5	25.25	26.5	28.0	29.25	30.25	32.0
11	22.25	24.5	26.0	27.25	28.5	30.25	31.0	32.25
12	19.25	21.25	22.75	23.25	24.5	26.0	27.0	27.25

TABLE IB

BODY WEIGHTS, POUNDS

Dog No.		Date					
		4/3	4/10	4/17	4/25	5/1	5/8
I.	Thiouracil						
	2	19.75	21.5	22.5	22.5	24.25	25.0
	3	33.25	34.0	35.0	35.5	36.75	37.0
	4	30.75	32.25	36.5	37.75	36.0	37.5
	5	13.5	14.0	14.5	14.75	14.75	15.0
II.	Control						
	6	31.0	33.0	35.0	36.5	37.0	37.0
	7	30.0	31.25	33.75	35.25	36.0	36.5
	8	29.25	30.75	33.25	35.0	35.75	36.0
	9	31.25	32.75	34.75	36.25	37.25	37.75
III.	Thyroidectomized						
	10	33.5	34.0	35.75	35.5	36.5	37.0
	11	33.75	35.75	38.25	40.25	41.0	41.5
	12	28.25	29.0	29.5	30.25	30.5	30.25

TABLE II

BODY WEIGHTS - GROUP AVERAGES, POUNDS

Group	Thiouracil	Control	Thyroidectomized
12/12	9.1±.7	10.0±.7	11.3±.8
12/19	9.7±.8	11.0±.8	11.5±1.0
12/26	10.7±.8	11.6±.8	12.4±.9
1/2	11.4±.7	12.9±.7	13.5±.9
1/9	13.0±1.1	14.6±1.1	14.6±1.3
1/16	14.8±1.2	16.6±1.2	16.3±1.4
1/23	15.3±1.4	17.3±1.4	17.3±1.6
1/30	16.3±1.5	18.6±1.5	18.9±1.7
2/6	17.8±1.7	20.3±1.7	21.0±2.0
2/13	18.8±2.0	21.9±2.0	23.0±2.3
2/20	19.4±2.0	23.4±2.0	24.8±2.3
2/27	20.0±2.1	24.4±2.1	25.7±2.4
3/6	20.9±2.3	25.7±2.3	27.0±2.7
3/13	21.9±2.6	27.1±2.6	28.5±3.0
3/20	22.4±2.6	27.6±2.6	29.4±3.0
3/27	23.1±2.6	28.9±2.6	30.5±3.0
4/3	24.3±3.0	30.4±3.0	31.8±3.4
4/10	25.4±3.0	31.9±3.0	32.9±3.5
4/17	27.1±3.4	34.2±3.4	34.5±3.9
4/25	27.6±3.6	35.8±3.6	35.3±4.1
5/1	27.9±3.5	36.5±3.5	36.0±4.0
5/8	28.6±3.6	36.8±3.6	36.3±4.1

± standard error

TABLE III

TIBIAL LENGTH, CENTIMETERS

Dog No.	12/12	1/20	2/20	3/20	4/20
I. Thiouracil					
2	9.1	12.0	13.6	13.8	14.7
3	8.6	14.5	15.2	16.3	16.6
4	9.3	13.0	14.7	15.4	16.0
5	9.7	10.2	10.3	10.7	11.3
II. Control					
6	9.0	15.6	17.3	18.3	18.8
7	8.8	15.8	17.4	18.3	18.9
8	9.3	16.0	17.4	18.4	19.0
9	9.7	15.2	16.9	17.9	18.3
III. Thyroidectomized					
10	9.7	14.4	15.2	16.0	16.9
11	9.8	15.2	16.5	17.5	18.2
12	10.2	13.0	14.3	15.1	15.5

TABLE IV

AVERAGE TIBIAL LENGTH

Group	12/12	1/20	2/20	3/20	4/10
Thiouracil	9.1±.6	12.4±.6	13.5±.7	14.1±.8	14.7±.8
Control	9.2±.6	15.7±.6	17.3±.7	18.2±.8	18.8±.8
Thyroidectomized	9.9±.7	14.2±.7	15.3±.8	16.2±.9	16.9±.9

± standard error

TABLE V

WIDTH, DISTAL EPIPHYSIS, TIBIA, CENTIMETERS

Dog No.		Date			
	12/12	1/20	2/20	3/20	4/10
I. Thiouracil					
2	1.7	1.7	1.9	2.0	1.8
3	1.3	2.2	2.4	2.4	2.3
4	1.9	2.0	2.2	2.2	2.2
5	1.6	1.6	1.5	1.6	1.9
II. Control					
6	1.4	2.4	2.2	2.2	2.3
7	1.5	2.4	2.2	2.1	2.2
8	1.5	2.0	2.2	2.0	2.0
9	1.6	2.2	2.3	2.3	2.0
III. Thyroidectomized					
10	1.9	2.0	2.3	2.4	2.3
11	1.8	2.2	2.4	2.4	2.2
12	1.9	2.1	2.1	2.0	1.9

TABLE VI

AVERAGE WIDTH, DISTAL EPIPHYSIS OF TIBIA (CENTIMETERS)

Group	Date				
	12/12	1/20	2/20	3/20	4/10
Thiouracil	1.6±.08	1.9±.08	2.0±.13	2.1±.13	2.1±.10
Control	1.5±.08	2.3±.08	2.2±.13	2.2±.13	2.1±.10
Thyroidectomized	1.9±.09	2.1±.10	2.3±.15	2.3±.15	2.1±.12

± standard error

TABLE VII

WIDTH OF TIBIAL DIAPHYSIS, CENTIMETERS

Dog No.	Date 12/12	1/20	2/20	3/20	4/10
I. Thiouracil					
2	0.8	0.9	0.9	1.0	1.0
3	0.7	1.1	1.2	1.2	1.2
4	1.0	1.2	1.2	1.2	1.4
5	0.8	0.8	0.8	0.8	0.8
II. Control					
6	0.8	1.2	1.3	1.3	1.3
7	0.7	1.1	1.2	1.2	1.3
8	0.7	1.2	1.2	1.2	1.4
9	0.8	1.2	1.2	1.2	1.4
III. Thyroidectomized					
10	0.8	1.1	1.2	1.2	1.3
11	0.8	1.0	1.2	1.3	1.3
12	0.8	1.0	1.0	1.1	1.2

TABLE VIII

AVERAGE WIDTH, TIBIAL DIAPHYSIS, CENTIMETERS

Group	Date				
	12/12	1/20	2/20	3/20	4/10
Thiouracil	.82±.04	1.0±.06	1.0±.07	1.1±.06	1.1±.08
Control	.75±.04	1.2±.06	1.2±.07	1.2±.06	1.35±.08
Thyroidectomized	.80±.05	1.0±.08	1.1±.08	1.2±.08	1.27±.09

± standard error

TABLE IX

ERUPTION TIME - SECONDARY DENTITION - THIOURACIL GROUP

Age in weeks	Dog No. 2	Dog No. 3	Dog No. 4	Dog No. 5
13				
14				
15		Cent. Lower I.*		
16		Cent. Lower I. Cent. Upper I.*		
17	Cent. Lower I. Cent. Upper I.*	Int. Lower I.		
18	Int. Lower I.	Cent. Upper I. Int. Upper I.	Cent. Lower I. Cent. Upper I.*	
19	Incisors Complete	Incisors Complete	Int. Lower I. Cent. Lower I.*	
20			Int. Upper I.	Cent. Lower I.
21			Incisors Complete	Cent. Upper I.* Int. Lower I.
22		Lower Canines Ret. Upper Canine		Int. Upper I. Cor. Upper I.*
23	Lower Canines		Lower Canines Ret.	Cor. Lower I.
24	Canines Complete			Incisors Complete
25		Canines Complete	Canines Complete	Canines not in at termination of experiment.

* Incomplete

TABLE X

ERUPTION TIME - SECONDARY DENTITION - CONTROL GROUP

Age in weeks	Dog No. 6	7	8	9
13	Cent. Lower I.		Cent. Lower I. Cent. Upper I.	
14	Cent. Upper I.	Cent. Lower I.	Int. Lower I. Int. Upper I.*	
15	Int. Lower I.	Cent. Upper I.		Cent. Lower I. Cent. Upper I.*
16	Incisors Complete	Int. Lower I. Int. Upper I.	Cor. Lower I. Incisors Complete	Cent. Upper I.* Int. Lower I.
17		Incisors Complete		Cor. Lower I. Int. Upper I.*
18				Incisors Complete
19				
20				
21				
22		Upper Canines*	Upper, Lower Canines*	
23	Upper, Lower Canines*	Lower Canines*		Upper, Lower Canines*
24	Canines Complete	Canines Complete	Canines Complete	
25				
26				Canines Complete

* Incomplete

TABLE XI

ERUPTION TIME - SECONDARY DENTITION - THYROIDECTOMIZED GROUP

Age in weeks	Dog No. 10	Dog No. 11	Dog No. 12
13			
14			
15			Cent. Lower I.
16			Cent. Upper I.
17		Cent. Lower I.	Int. Upper I.
			Int. Lower I.
18		Cent. Upper I.	
	Cent. Lower I.	Int. Lower I.	Lower Cor. I.*
19	Cent. Upper I.	Incisors Complete	Incisors Complete
20	Int. Lower I.		
	Int. Upper I.*		
21	Incisors Complete		
22			
23	Lower Canines		Lower Canines*
24	Canines Complete	Canines Complete	Canines Complete

* Incomplete

TABLE XII

BODY TEMPERATURES, DEGREES F.

Dog No.	Date 12/12	12/19	1/2	1/9	1/16	1/23	1/30	2/6
I. Thiouracil								
2	101.8	102.0	101.6	102.0	102.4	102.0	102.0	101.6
3	101.2	102.0	102.0	101.8	103.0	102.8	103.0	102.6
4	102.0	101.8	102.4	102.0	101.6	101.8	102.4	102.6
5	101.8	101.8	102.4	102.4	102.0	101.6	102.2	102.4
II. Control								
6	102.0	101.8	101.6	102.6	102.0	102.4	102.8	102.8
7	102.2	101.2	101.6	102.0	102.4	103.2	103.2	103.8
8	101.6	102.0	102.0	102.4	102.2	103.4	103.4	104.0
9	101.4	102.0	102.4	102.0	102.4	103.6	102.4	102.6
III. Thyroidectomized								
10	101.8	101.8	102.0	101.4	102.0	102.0	102.6	102.4
11	102.0	102.0	101.4	102.2	101.8	102.2	102.0	102.4
12	101.6	102.4	101.8	102.0	101.8	101.8	102.0	101.8

TABLE XIIA

BODY TEMPERATURES, DEGREES F.

Dog No.	Date 2/13	2/20	2/27	3/6	3/13	3/20	3/27	4/3	4/10
I. Thiouracil									
2	101.4	102.0	101.8	102.0	101.4	101.8	102.6	102.2	102.4
3	102.8	103.2	102.8	103.0	102.8	103.2	102.8	103.6	103.0
4	103.0	102.6	102.4	102.4	104.2	102.8	103.0	102.8	103.0
5	102.2	101.8	102.6	102.4	103.0	102.2	102.2	102.4	101.6
II. Control									
6	102.8	102.8	103.4	103.0	103.4	102.6	103.6	103.4	103.2
7	103.4	103.2	103.6	103.6	103.8	103.2	102.8	103.0	103.2
8	103.2	103.0	104.0	103.4	104.6	103.2	105.0	103.8	103.6
9	102.4	103.2	102.4	102.4	102.0	102.3	103.2	102.8	103.0
III. Thyroidectomized									
10	102.2	102.6	102.4	102.2	103.2	102.0	103.0	102.8	102.6
11	102.0	102.2	101.8	102.0	102.2	102.0	102.4	102.2	102.4
12	101.6	101.6	101.6	101.8	102.0	101.8	102.0	101.8	101.6

TABLE XIII

PULSE RATES, COUNTS PER MINUTE

Dog No.	Date 1/20	1/29	2/5	2/12	2/19	2/26	3/6	3/13	3/20
I. Thiouracil									
2	80	160	152	112	140	136	134	128	122
3	96	120	120	148	140	160	144	136	120
4	108	128	138	140	120	124	128	120	132
5	126	120	128	100	104	112	116	112	142
II. Control									
6	100	140	156	140	140	144	140	142	138
7	120	128	140	144	140	148	140	148	142
8	112	140	128	140	136	132	128	112	136
9	104	136	132	128	136	132	128	132	119
III. Thyroidectomized									
10	120	140	148	128	140	152	148	158	120
11	112	124	128	112	120	128	124	128	118
12	116	120	128	100	120	120	124	128	112

TABLE XIV

PULSE RATES - AVERAGE WEEKLY

Date	Group		
	Thiouracil	Control	Thyroidectomized
1/20	103±7	109±7	116±8
1/29	132±7	136±7	128±8
2/5	135±6	139±6	135±7
2/12	125±9	138±9	113±10
2/19	126±6	138±6	127±7
2/26	133±8	139±8	133±9
3/6	130±6	134±6	132±6
3/13	124±9	133±9	138±11
3/20	129±5	134±5	117±5

± standard error

TABLE XV

FOOD INTAKE PER WEEK, IN POUNDS (APPROXIMATE)

Week	Thiouracil				Control				Thyroidectomized		
	2	3	4	5	6	7	8	9	10	11	12
2	8.5	8.5	8.5	8.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
3	10.15	10.15	10.15	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
4	8.0	10.5	10.5	7.0	10.5	10.5	10.5	10.5	10.5	10.5	10.5
5	*6.5	10.5	10.5	8.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
6	14.0	14.0	14.0	*5.0	14.5	14.5	14.5	14.5	14.5	14.5	14.5
7	*7.0	21.0	21.0	*6.0	14.5	17.5	21.0	17.5	*7.0	21.0	21.0
8	8.75	21.0	17.5	*7.5	17.5	17.5	21.0	14.5	17.5	21.0	21.0
9	10.5	21.0	14.0	*5.0	21.0	21.0	21.0	17.5	17.5	17.5	21.0
10	14.0	21.0	17.5	*7.0	21.0	21.0	21.0	21.0	21.0	21.0	21.0
11	14.0	21.0	17.5	7.5	21.0	21.0	21.0	21.0	21.0	21.0	21.0
12	*9.0	14.5	14.0	10.0	17.5	21.0	21.0	21.0	21.0	21.0	21.0

TABLE XV (Continued)

Week		Thiouracil				Control			Thyroidectomized		
	2	3	4	5	6	7	8	9	10	11	12
13	14.0	16.5	21.0	6.0	17.5	21.0	21.0	21.0	21.0	21.0	21.0
14	14.5	21.0	21.0	*5.5	15.5	21.0	21.0	21.0	21.0	21.0	21.0
15	14.0	14.0	17.5	7.5	17.5	21.0	21.0	21.0	21.0	21.0	21.0
16	12.0	14.0	21.0	7.5	21.0	21.0	21.0	21.0	21.0	21.0	21.0
17	14.5	17.5	21.0	10.0	21.0	21.0	21.0	21.0	21.0	21.0	21.0
18	16.0	16.5	17.5	10.5	21.0	21.0	21.0	21.0	21.0	21.0	21.0
19	14.0	17.5	14.0	12.5	21.0	21.0	21.0	21.0	21.0	21.0	21.0
20	14.0	17.5	14.0	12.5	21.0	21.0	21.0	21.0	21.0	21.0	21.0
21	16.5	14.0	17.5	10.5	21.0	21.0	21.0	21.0	21.0	21.0	21.0

* consumed liquids only

TABLE XVI

BLOOD EXAMINATION

Group	R.B.C.	W.B.C.	Hb. (Gm.)	Cell Volume	Sedimentation Time 30min.	60min.
I. Thiouracil						
2	5,040,000	13,000	12.9	26.5	1	3
3	3,750,000	15,900	13.6	32.5	4	11
4	4,290,000	13,950	11.5	27.0	2	10
5	3,880,000	8,300	9.0	22.5	1	15
II. Control						
6	6,370,000	10,250	17.9	45.0	.25	0.5
7	7,990,000	14,100	19.9	50.0	0	0.5
8	6,500,000	10,500	17.3	45.5	0.5	1.0
9	6,600,000	11,950	17.3	42.0	0.25	1.0
III. Thyroidectomized						
10	6,870,000	13,900	17.9	45.5	0.25	0.5
11	5,130,000	11,850	17.3	37.0	0.5	1.5
12	5,460,000	9,600	16.8	38.0	0.25	0.5

TABLE XVI (Continued)

Differential Counts - Percent

Group	Neutrophils Seg.	Neutrophils Non-Seg.	Lymph	Mono	Eosin	Baso
I. Thiouracil						
2	27	8	59	4	1	1
3	29	19	48	1	3	0
4	55	20	22	0	0	3
5	47	22	26	2	2	1
II. Control						
6	37	27	34	2	0	0
7	52	29	18	1	0	0
8	36	42	20	2	0	0
9	35	31	30	2	2	0
III. Thyroidectomized						
10	37	23	36	2	2	0
11	35	36	25	0	2	2
12	47	26	23	0	2	2

TABLE XVII

I^{131} UPTAKE (COUNTS PER MINUTE)**

Dog No.	5 min. Thy*	5 min. Ext*	12 hr. Thy	12 hr. Ext	24 hr. Thy	24 hr. Ext	48 hr. Thy	48 hr. Ext	72 hr. Thy	72 hr. Ext	170 hr. Thy	170 hr. Ext
I. Thiouracil												
2	1840	210	1605	580	1710	410	385	110	350	80	35	10
3	1835	335	1580	480	660	160	425	120	310	30	20	20
4	2080	380	850	250	1110	160	330	80	135	45	10	10
5	860	335	650	225	450	150	265	50	150	50	0	0
II. Control												
6	430	330	1650	200	2265	105	2200	50	2720	40	1190	0
7	550	400	1900	200	2525	120	2410	35	2420	10	1530	0
8	500	400	1960	310	2130	90	2100	40	2610	0	1165	20
9	680	480	1470	220	2730	580	2140	25	2325	15	1160	15
III. Thyroidectomized												
10	430	630	650	450	525	200	320	65	65	35	0	0
11	480	530	525	500	850	400	525	100	430	65	40	10
12	430	380	460	335	480	130	450	100	250	50	15	15

** Counts corrected for background

Thy* Thyroid
Ext* Extremity

TABLE XVIII

AVERAGE I^{131} UPTAKE*

	Thiouracil	Control	Thyroidectomized
5 min.			
Thy.	1654±169	540±169	447±195
Ext.	315±42	403±42	513±50
12 hr.			
Thy.	1220±178	1818±178	568±205
Ext.	400±62	242±62	446±71
24 hr.			
Thy.	1080±68	2651±68	680±78
Ext.	242±49	246±49	268±57
48 hr.			
Thy.	418±64	2633±64	574±74
Ext.	107±14	45±14	105±16
72 hr.			
Thy.	307±102	3272±102	323±118
Ext.	67±11	21±11	65±13
170 hr.			
Thy.	31±104	2380±104	34±121
Ext.	19±10	17±10	16±11

* Corrected for background and decay.

± Standard error

TABLE XIX

CELL PLASMA I^{131} RATIOS

Dog No.	Time, Post-Injection 5 min.	12 hr.	24 hr.	48 hr.	72 hr.
I. Thiouracil					
2	1.73	.63	.33	.36	.45
3	1.30	1.01	.37	.28	---
4	1.43	1.49	.49	.38	.43
5	2.29	3.45	.48	.43	.43
II. Control					
6	1.02	1.01	.38	. 27	.26
7	.78	1.51	.30	.27	.12
8	1.19	.60	.37	.35	.0019
9	.78	.76	.34	.32	.058
III. Thyroidectomized					
10	.69	.69	.32	.26	.26
11	.88	.24	.32	.20	.19
12	.70	.24	.28	.36	.24

TABLE XX

AVERAGE RATIOS, CELL PLASMA I^{131}

Group	Time Post-Injection				
	5 min.	12 hr.	24 hr.	48 hr.	72 hr.
Thiouracil	$1.69 \pm .15$	$1.65 \pm .41$	$.42 \pm .032$	$.38 \pm .032$	$.44 \pm .039$
Control	$.94 \pm .15$	$.97 \pm .41$	$.35 \pm .032$	$.30 \pm .032$	$.1025 \pm .039$
Thyroidectomized	$.76 \pm .18$	$.39 \pm .47$	$.31 \pm .036$	$.27 \pm .036$	$.23 \pm .045$

$\pm$ standard error

FIGURE IX, Dog No. 2

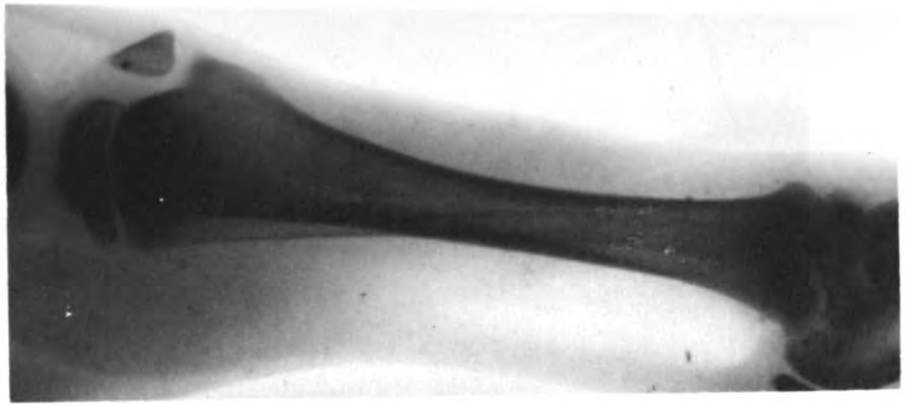
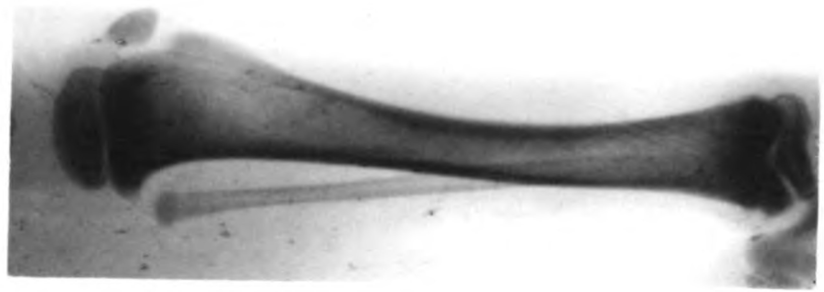


FIGURE X, Dog No. 3



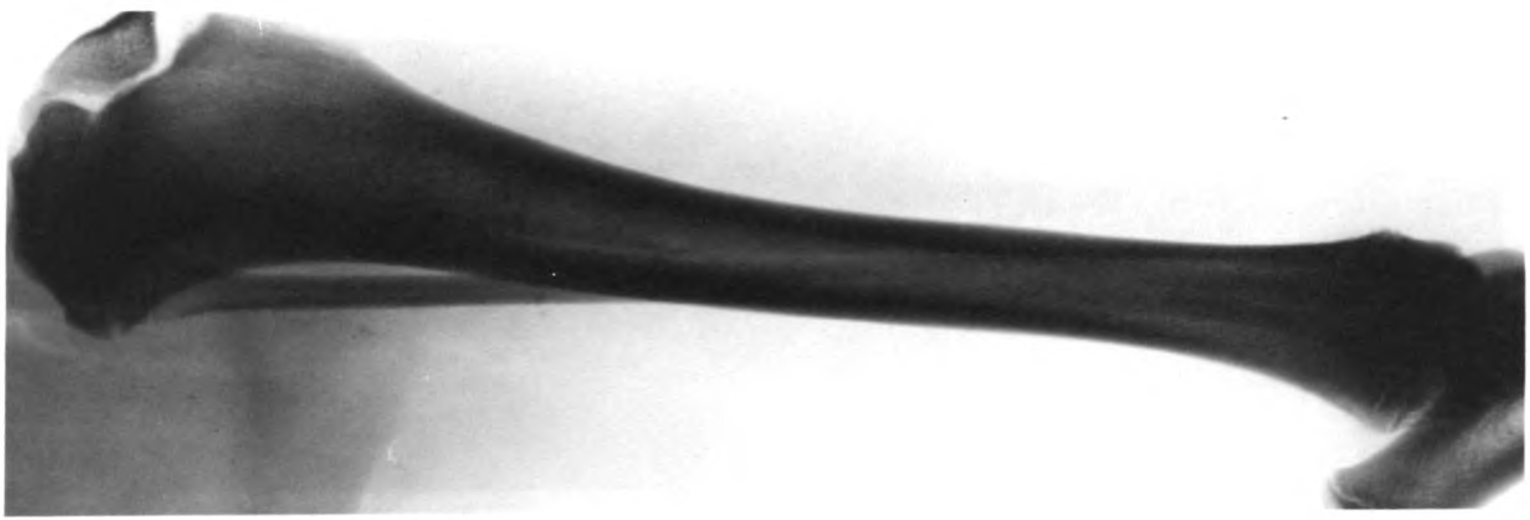


FIGURE XI, Dog No. 4

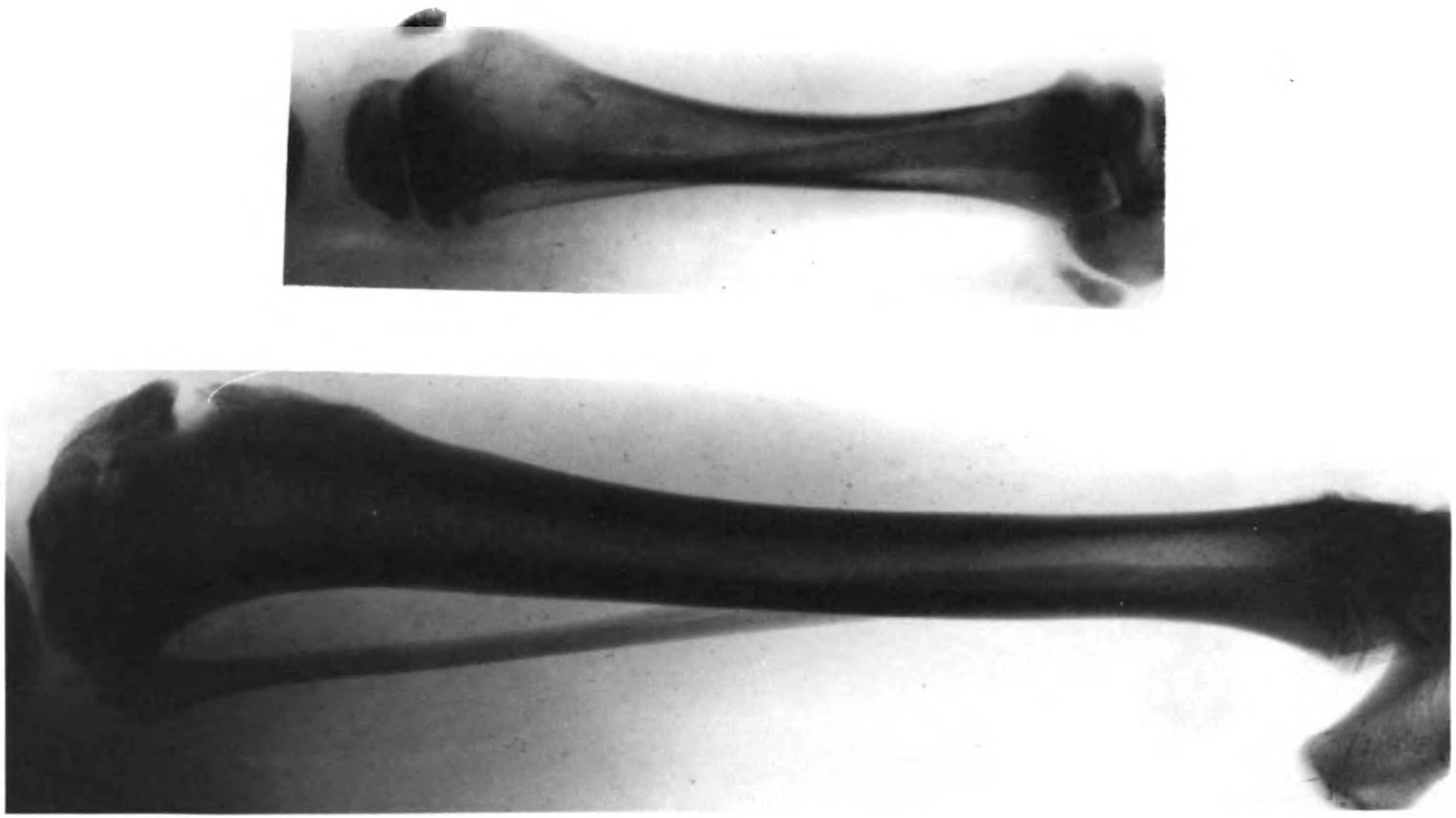


FIGURE XII, Dog No. 5

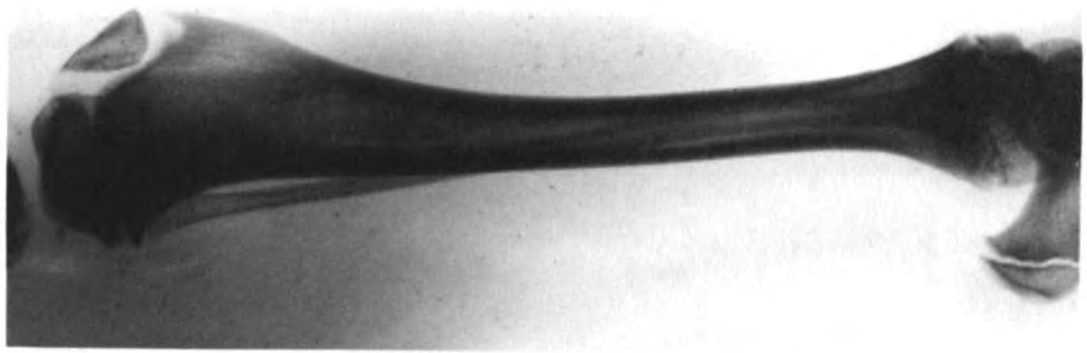
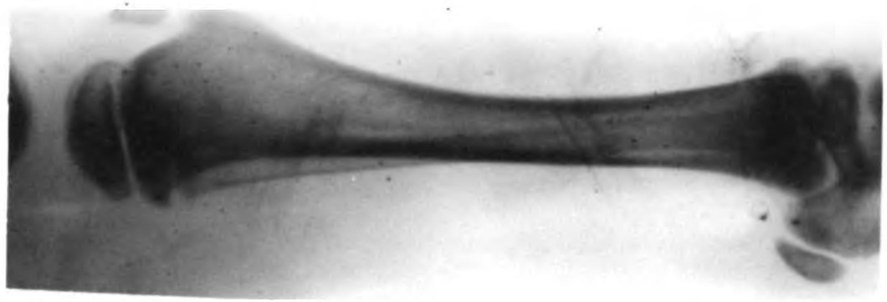


FIGURE XIII, Dog No. 6



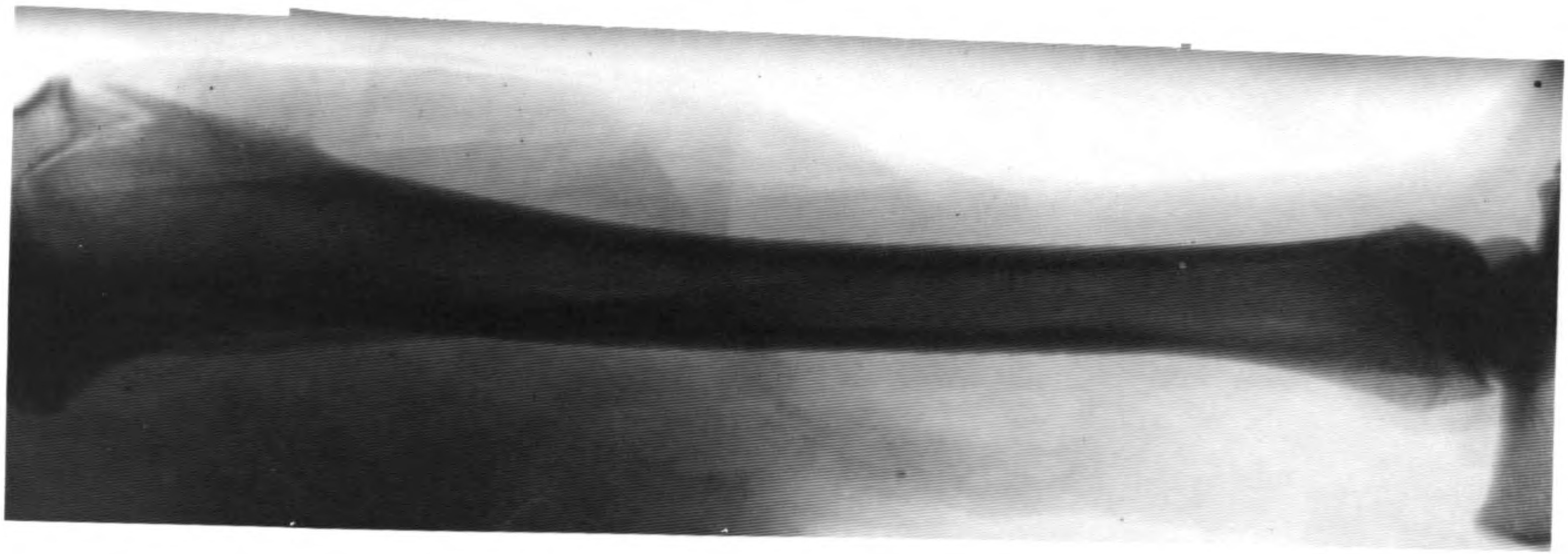


FIGURE XIV, Dog No. 7

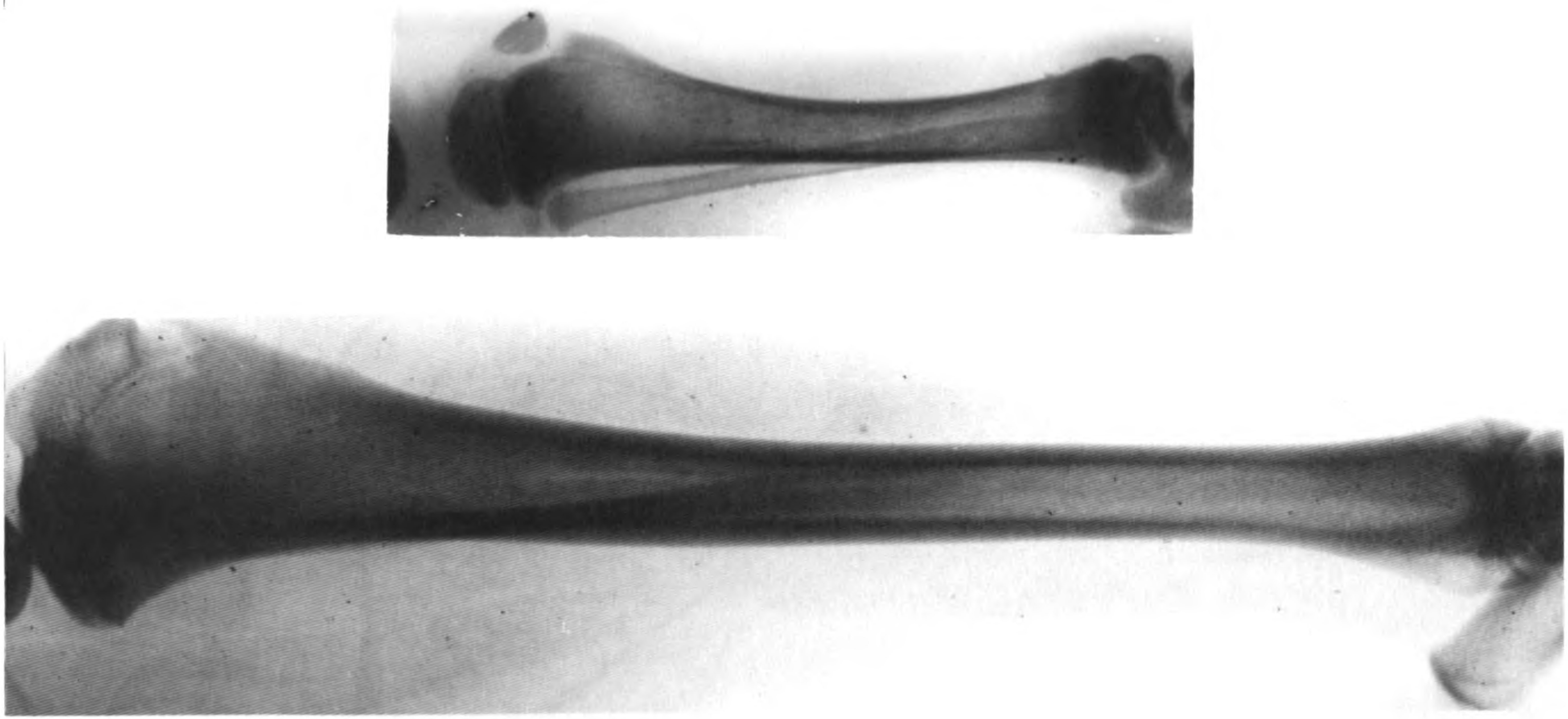
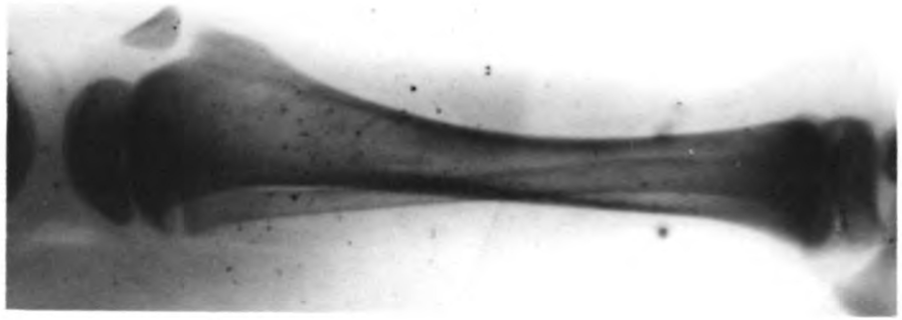


FIGURE XV, Dog No. 8



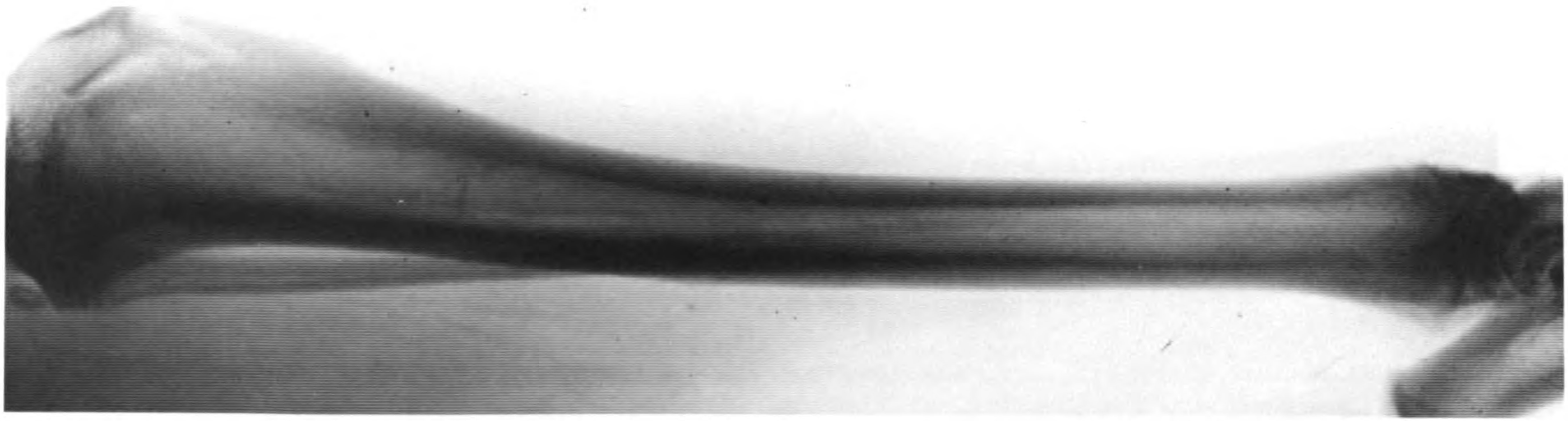


FIGURE XVI, Dog No. 9

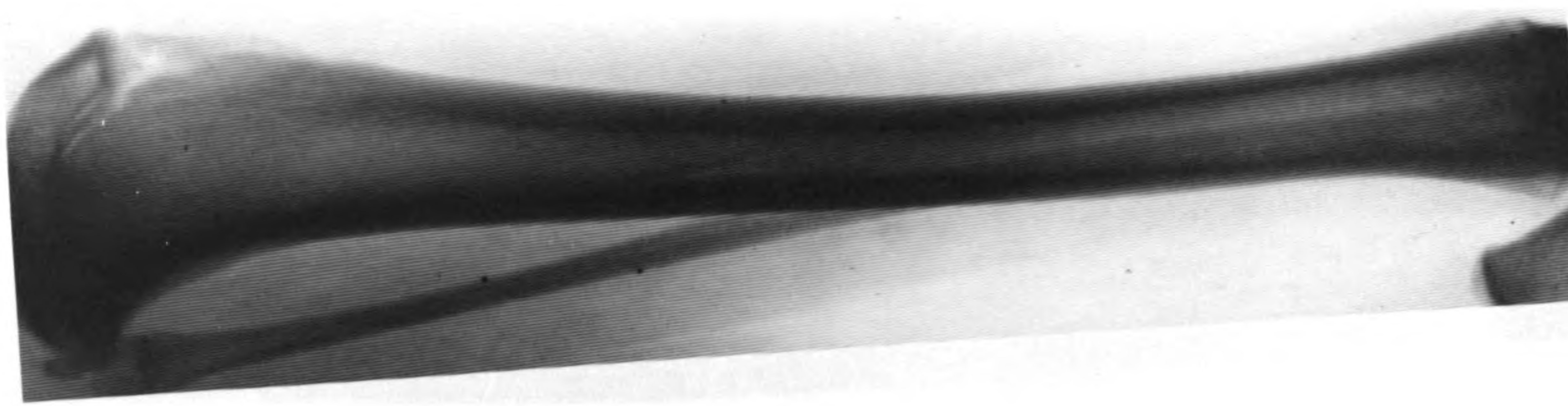


FIGURE XVII, Dog No. 10

FIGURE XVIII, Dog No. 11

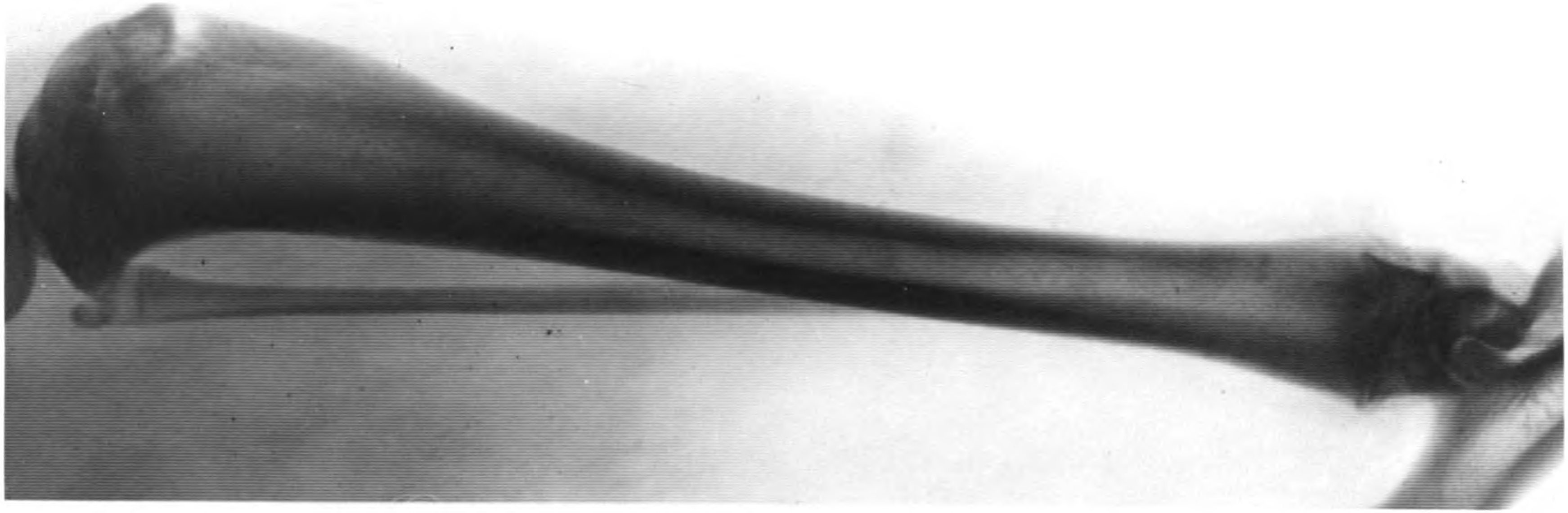


FIGURE XIX, Dog No. 12