SOME ENDOCRINE ASPECTS OF DWARFISM

IN BEEF CATTLE

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INTRODUCTION

Attention has been focused on an hereditary type of dwarfism which has occurred in all of the major breeds of beef cattle within the past few years. Most of the evidence indicates that the hereditary nature of this trait is rather simple, perhaps being conditioned by a single pair of autosomal recessive genes. The rapid increase in the frequency of these dwarf calves has led some people to believe that the heterozygous animals are being favored in selection over the homozygous normal animals. This, of course, suggests that the two types are distinguishable. Proof of this point is lacking, however. If this is true and if the breeders are unconsciously favoring those animals which carry the dwarf-producing gene in a heterozygous condition, theoretically this would in time increase the frequency of dwarf calves to 25 per cent of the total calf crop. Obviously, this would amount to a greater economic loss than the beef cattle industry could afford.

Therefore, it becomes extremely important that some method be devised for detecting the potential dwarf producers so that they may be eliminated from the breeding herds. This could be done by progeny testing, but it would be very expensive and time-consuming and not at all practical, except for testing the most valuable purebred bulls. Therefore, some phenotypic indicator is needed to identify these heterozygous individuals. Although the hereditary nature of dwarfism in beef cattle appears to be fairly well established, there has been no satisfactory explanation of the abnormal physiological action of the dwarf gene. The literature on the subject strongly implicates the anterior pituitary as the responsible organ.

Hereditary types of dwarfism have been known for many years in many different species of plants and animals. There are reports of dwarfism in most of the animal species, including rabbits, mice, guinea pigs, poultry, swine, sheep, goats, dogs, cattle, and man. Dwarfism in mice and certain types of dwarfism in humans have been shown to be due to a deficiency of growth hormone produced by the adenohypophysis. Cretinism in humans and experimental cretinism in animals results from a thyroxin deficiency as a result of hypofunction of either the pituitary or the thyroids.

Since it is known that dwarfism in many species is mediated through the endocrine organs, it was felt that a study of some of the endocrine aspects in dwarf calves, and of the hormonal activity of the anterior pituitary in particular, might bring to light some of the abnormal physiological actions of the dwarf-producing genes. If a gross deficiency of one or more of these hormones could be demonstrated in the dwarf calves, it might be possible to devise inexpensive tests based on the activity of this gland or hormone which would distinguish between the normal and "carrier" animals.

Based on this reasoning, a study was conducted to determine (1) if there are endocrine abnormalities in the dwarf calves, (2) whether or not the same mechanisms are responsible for the different types of dwarfism among the different breeds, and (3) whether or not normal and "carrier" animals may be accurately identified on the basis of the information gained from these studies.

A DESCRIPTION OF THE DWARF CALF

No dwarf calf is likely to express all of the symptoms associated with dwarfism. Neither is any one symptom likely to be expressed in all dwarf calves. However, there are certain characteristics which are common to most dwarf calves and which should be helpful in correctly identifying these calves at birth or shortly thereafter. It should be pointed out that dwarf calves vary not only in the kinds of abnormalities but also in the degrees of expression of these abnormalities. The expression of dwarfism ranges from prenatal death and abortion of the fetus through various degrees of abnormalities to animals which are only slightly abnormal and perhaps may even be able to reproduce and maintain a nearly normal existence.

One of the traits most often noted is an abnormality of the head. Most dwarfs have bulging foreheads, short, wide muzzles, protruding lower jaws,and prominent eyes. Some of these calves have a very "blocky build" at birth, being extremely short-legged, heavy-boned, and thick, and may be mistaken for a normal calf by someone unfamiliar with dwarfism. Many of the dwarf calves are weak at birth and may have to be assisted in nursing. They often have poor co-ordination and weave about while walking. Some have extremely crooked legs, particularly those of compresst Hereford breeding. Angus dwarfs appear to be more irritable than normal calves but few of them lack co-ordination of movement. Most dwarfs do not live for more than a few months. Those that live quite often gain weight and fatten fairly rapidly for the first two or three months, after which they usually develop a "pot-belly" and begin to lose

flesh. Most of them also develop heavy or labored breathing by this time. By the time these calves are old enough to start eating solid feeds they usually become chronic bloaters, and many die as a result. Nearly all of the reports on dwarfism point out the digestive disturbances noted in these animals.

Many of the dwarf calves show evidence of an internal hydrocephalus; however, this is not found in all cases. The main abnormalities appear to involve skeletal development. There is definitely abnormal vertebral formation. The vertebrae of dwarfs have ragged edges and convex vertral surfaces instead of the smooth, concave surfaces of the vertebrae in normal calves. The long bones of the body are shorter and thicker than those of normal calves. Many of these calves exhibit symptoms similar to those noted in rickets. As the dwarf calves grow older, the dwarf characteristics usually become more pronounced. They lose flesh, and the carcass is of poor quality.

The great variation in the expression of dwarfism in beef calves is depicted in the series of pictures shown on the following pages:

Plate 1: This picture shows the extreme expression of dwarfism in a $2\frac{1}{2}$-month-old Hereford female of compromise breeding. This calf required assistance while nursing and weighed 77 pounds.

Plate 2: A 1-month-old Angus dwarf. Note the extremely dished face and bulging forehead.

Plate 3: A 16-month-old Hereford steer with typical features of dwarfism. Note the protruding underjaw, dull expression, and bloated condition.

Plate 4: A group of Angus and Hereford dwarfs from 4 to 6 months of age. Note the thickness of these calves. Note also their short, broad heads and short legs.

Plate 5: A crossbred calf out of a compromise Hereford cow and by an Angus bull. This calf was a chronic bloater and weighed only 100 pounds at 4 months of age.

Plate 6: A 3-month-old bull calf out of a grade Hereford cow. Note the humped back and the extremely thin condition. Calf weighed 110 pounds.

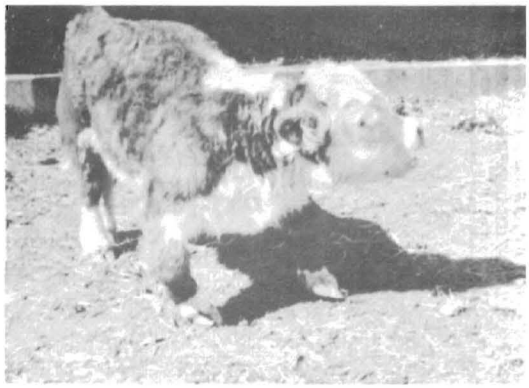
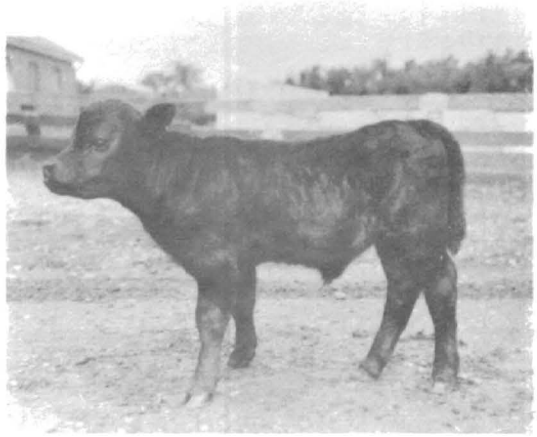


Plate 1



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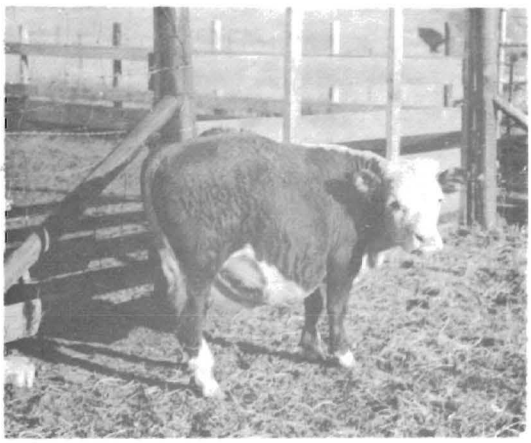

Plate 3

Plate 4

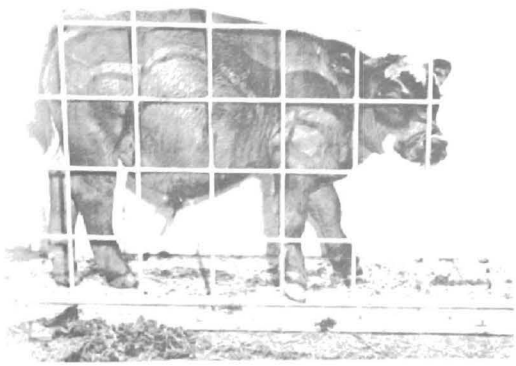

Plate 5

Plate 6

Plate 7: A 2½-year-old dwarf Hereford bull, weight 525 pounds and height approximately 30 inches. Note the straight face, well developed gonads and thickness of this animal. Note that this bull is not as tall as the 4-month-old normal bull in Plate 11.

Plate 8: A 2½-year-old dwarf Hereford cow, weight 425 pounds. A calf was taken from this cow by Caesarean operation about 3 weeks prior to taking this picture. The calf died from strangulation. It was supposedly sired by the bull shown in Plate 7.

Plate 9: A 4-month-old Hereford heifer believed to be homozygous normal. Weight 290 pounds.

Plate 10: A 4-month-old dwarf heifer that was a half-sister to the heifer shown in Plate 9. Weight 190 pounds.

Plate 11: A 4-month-old Hereford bull calf believed to be free of the dwarf gene. Weight 260 pounds.

Plate 12: A 4-month-old dwarf bull calf that was a half-brother to the bull calf shown in Plate 11. Weight 160 pounds.

Plate 7

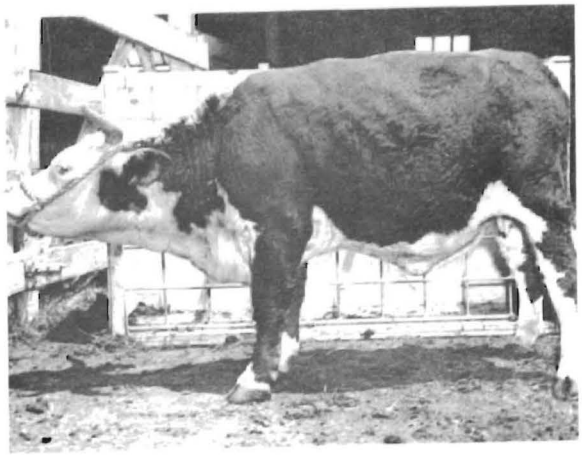

Plate 8

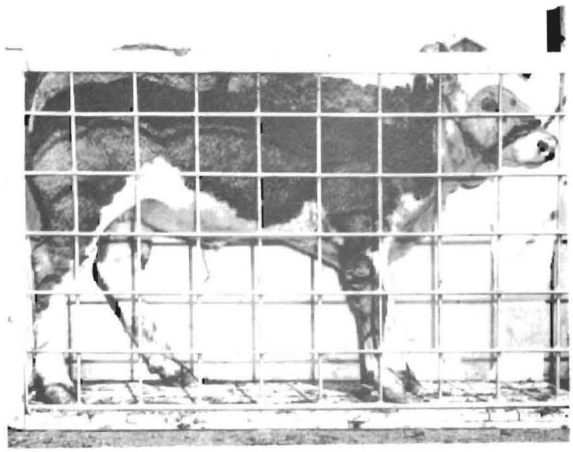

Plate 9

Plate 10

Plate 11

Plate 12

REVIEW OF STUDIES ON DWARFISM AND RELATED PHENOMENA

Dwarfism in Cattle

Dwarfism has been reported in all of the major breeds of beef cattle. Perhaps the first report of the type of dwarfism with which we are presently concerned was that of Craft and Orr (1924). They described a dwarf calf dropped in Oklahoma in 1923 that exhibited symptoms similar to cretinism in man, "a general dwarf-like appearance, short and irregularly curved legs, abnormally large joints, short and thickened face and a nervous disposition." This animal weighed only 330 pounds at 9 months of age. At autopsy they found the thyroid, parathyroids, and pituitary glands greatly underdeveloped. The thyroids were only one-fifth the normal size, but the pituitary was about one-half normal size. The bones lacked firmness, and the ends of the long bones were somewhat enlarged. They believed this dwarfed condition was due to a deficiency of the thyroid and pituitary secretions.

Johnson et al (1950) described a type of dwarfism in Hereford cattle which they classified as a latent lethal because most of these animals died before reaching maturity. This was probably the same type as described earlier by Craft and Orr. At birth these calves were not very different from normal calves except that they appeared to be slightly wider and blockier. The dwarf characteristics became more pronounced with age. (This type of dwarf calf was described earlier in this paper.) Autopsy of these calves at the younger ages failed to reveal anything grossly different from normal calves; however, the lateral ventricles of the brain contained more than the normal amount of fluid. Histological sections of the endocrine organs showed nothing abnormal. The thyroids

were in an active state, and spermatozoa were found in the ampulla of the ductus deferens, but there was very little spermatogenesis occurring in the tubules of the testes.

In the same year Baker et al (1950) described a recessive form of achondroplasia in Shorthorn cattle that they called "stumpy". These animals were characterized by a curly coat (which made them easily identified at birth), smaller switch, and achondroplastic conditions of enlarged knees, slightly twisted cannon bones, enlargement of the hoof-head, and a rotation outward of the feet. They were also dwarfed in size and apparently troubled with metabolic disturbances as indicated by a poor condition that increased with age. This condition was not lethal, however, and the animals reproduced. They did not study the physiological processes involved. Baker et al (1951) also reported an autosomal recessive type of dwarfism in Aberdeen-Angus cattle which was very similar to that of the Hereford dwarfs reported by Johnson et al (1950). These dwarfs were not always distinguishable from normal calves at birth. They usually exhibited exceptionally compact, low-set, thick bodies, with short, wide heads. However, they did not usually gain and fatten normally, and after a few months they lost much of the thickness and finish exhibited at the earlier age.

Carroll et al (1951) and Gregory et al (1951, 1953) concluded from studies on the type of dwarfism described in Hereford cattle that it was due to a deficiency of the thyrotropic hormone of the anterior pituitary. According to these writers the most outstanding characteristic of this type of dwarfism was a brachycephalic head with a marked mid-forehead prominence which was present at birth and persisted throughout the life of the individual. Other characteristics included a protruding underjaw, a slightly greater body width in proportion to length which approached

that of a mature animal rather than a calf, labored breathing, and a "pot-belly" at two or more months of age. They concluded that all of these characteristics were symptoms of thyroid deficiency and the morphological manifestations of the syndrome of cretinism. They believed that the heterozygote could be distinguished by the breeder and was preferred over the homozygous normal animals. They felt that this preference had led to an increased frequency of the dwarf gene. They reported that the dwarf gene was expressed in the heterozygous state by a marked effect on the frontal bones so that such "carrier" animals could be differentiated from homozygous normal animals with a high degree of accuracy by measuring this deviation of the skull. This median prominence was thought to be brought about by a hypofunction of the thyroid gland which was gene specific and conditioned solely by the dwarf gene. Consequently, they based their program of identification of the heterozygote by the use of a "profilometer" on the assumption of a thyrotropic deficiency, which indirectly through the thyroid gland produced a characteristic skull shape.

Histological studies of the endocrine glands by Gregory *et al* (1951, 1953), Johnson *et al* (1950), and Lindley (1951) have failed to show any abnormalities with the exception of cystic spaces in the pituitary found by Lindley and very little spermatogenesis in the tubules, with few sperm and hypoplasis of the germinal epithelium and interstitial cells found by Lindley (1951) and Johnson *et al* (1950). Stonaker and Wheeler (1950) found no differences in the pituitary and thyroid glands from large and small type cattle from histological studies.

This type of dwarfism has been shown to be conditioned by a single pair of autosomal recessive genes by Baker *et al* (1950, 1951), Carroll *et al* (1951), Gregory *et al* (1951, 1953), and Lush and Hazel (1952).

A review of the studies on the genetic aspects of dwarfism in beef cattle has been presented by Chambers, Marlowe and Whatley (1954).

Lush (1930) described a form of "duck-legged" cattle on Texas ranches that were Herefords in every respect except that their legs were about four inches shorter than the legs of normal Herefords. He believed that this "duck-legged" trait was transferred to Hereford cattle from the Dexter-Kerry cattle of Ireland. However, mating of these cattle produced no "bull-dog" calves nor extreme dwarfs that were common when Dexter cattle were mated together. Microscopic examination of the glands showed no abnormalities. He concluded that the condition was due to a single autosomal dominant gene with incomplete penetrance.

Lerner (1944) listed 25 hereditary lethal conditions in cattle, some of which were due to malfunctions of the endocrine system. Johansson (1953) briefly reviewed several types of inherited skeletal abnormalities in cattle. The "bull-dog" calf of the Dexter breed was described as early as 1904. These monsters were usually aborted after 6 to 8 months of pregnancy. They had extremely short limbs, bulging crania, depressed noses, and protruding lower jaws. The tail head was far up on the back,and there was usually a large umbilical hernia. This lethal was caused by a dominant gene in the homozygous state. It also had a marked effect in the heterozygote. Crew (1923) concluded that the"Dexter-monsters" resulted from a malfunctioning of the pituitary between the second and third months of intra-uterine life. Downs (1928) reported the occurrence of a "Dexter-monster" in a Jersey-Holstein cross. The monster had no hard palate, no pituitary,and only one parathyroid gland. The thyroids were small but the thymus was large and active. He concluded that the condition was hereditary and involved the endocrine system. Other "bull-dog" calves have been reported by Wriedt and Mohr (1928), Punnet (1936),

Brandt (1941), Surrarrer (1943), and Berger and Innes (1948).

Johansson (1953) described a new type of achondroplasia in Swedish cattle in which 25 of the 53 calves sired by one bull were malformed. The type and behavior of one of the malformed bull calves indicated endocrine disturbances. The four heifers available for study also showed signs of endocrine disturbances such as reproductive failures, small udders, and low milk yield. They assumed that these defective animals were heterozygous for a gene for achondroplasia and that this gene had arisen by mutation in the pregerminal tissue of the sire.

Cole (1942) reported a case of hydrocephalus in Holstein-Friesian cattle which he believed was due to an autosomal recessive gene. This gene was lethal and caused a marked enlargement of the skull, twisted condition of the forelegs, abnormal mandibles and asymmetry of the face, extremely wide hips, and short, thick humeri and femurs with large joints.

Mead et al (1942) reported a new type of proportionate dwarfism in a herd of Jersey cattle in California. These dwarfs were not distinguishable at birth but they grew more slowly and were distinguishable at one year of age. At maturity the dwarfs were from 150 to 200 pounds lighter than normal cows. They also averaged 10 to 12 centimeters lower at the withers and 10 centimeters smaller in heart circumference than their normal half sibs. The inheritance of this type of dwarfism appeared to be due to a simple autosomal recessive factor. These same workers reported a recurrent mutation of dominant achondroplasia in a herd of Jersey cattle which reduced the skeletal development. The heterozygous animals were easily distinguishable by their short legs. The mutant gene affected both the length of the limbs and spinal elements so that there was no overlapping in heights of the mutant and normal types.

All mutant types were descended from a single bull whose parents were both normal. All daughters of this bull were high producers. The homozygous mutants show a marked achondroplasia which was lethal and which appeared to be identical with the Dexter type of homozygous dominant achondroplasia.

Gregory et al (1942) reported a new type of recessive achondroplasia in the Jersey herd of the California Experiment Station. The expression was extremely variable but was usually lethal. Both axial and appendicular skeletal structures might be affected. All defective animals had short, broad heads and abnormal maxilla.

Eaton (1937), in a summary of lethal factors in cattle, listed achondroplasia, ossification of the joints, skin deformities, short limbs, mummification, and short spine, most of which were reportedly due to simple recessive lethal factors. He defined a lethal factor as one which eventually leads to the death of the organism as a result of the defect it produces.

Brody and Frankenback (1942) and Spielman et al (1945) were able to produce cretinism in dairy cattle by thyroidectomy at an early age. The former workers thyroidectomized 6 Jersey calves at various ages, but only one lived. The others died at ages ranging from 3 weeks to 5 months postoperative. The immediate causes of death were colds, pneumonia, and bloat. The calf that lived was thyroidectomized at the oldest age of 54 days. She had not shed her calf coat at 40 months, and her weight was 480 pounds. Her height was only 41.6 inches. She had stiff, large, bony ankles, a large paunch, an extremely dished face, and she was constipated from approximately one month following thyroidectomy. Her BMR was low, and she was extremely sensitive to cold.

Spielman et al (1945) studied the effects of thyroidectomy on the general appearance, growth and reproductive performance in dairy cattle. Thyroidectomized yearling cattle began to show symptoms about two months postoperative. The hair became progressively dry and brittle, the skin thick and dry, the limbs swollen, and the movements slow and clumsy. There was difficulty in walking, with a peculiar shuffling gait. They spread their legs to form a broad base while standing. Marked enlargement of the hocks became evident at about four months following removal of the thyroids. Marked intraperitoneal bloat was observed about three months postoperative that persisted until death due to an accumulation of fluid in the peritoneal cavity. Appetite was decreased, and constipation became chronic. These changes were reported as typical of bovine cretinism. Thyroidectomy of a cow at 45 months of age had little effect on general body conformation and appearance except for an increased accumulation of fat.

They reported that thyroidectomy was followed by impairment of the normal growth processes. There was a complete stasis of height gain and severe retardation in body weight gain. During pregnancy, however, there was a resumption of growth and when thyroidectomy was performed on a pregnant animal the characteristic symptoms failed to appear.

These workers also reported that thyroidectomy apparently did not impair the process of gametogenesis either in the male or the females. However, it caused a total loss of libido in both sexes. Oral administration of fresh thyroid restored the mating desire and increased milk and butter fat yield.

Dwarfism in Humans

It gradually became apparent to clinicians that certain types of human dwarfism were associated with an underactivity of the anterior lobe of the pituitary gland (Turner, 1953). Presumably the specifically damaged elements in the pituitary were acidophilic cells which secrete the hormone regulating growth.

According to Friedgood (1946), dwarfism per se refers to the diminutive stature, and may be due to one or more of many causes, such as: genetic variation secondary to germinal defects, adenohypophyseal deficiencies secondary to various types of tumors, congenital or acquired hypothyroidism, hypophyseal infection, severe nutritional deficiencies, and chronic heart disease acquired congenitally or in infancy.

Freeman (1950) stated that underactivity of the growth-promoting factor of the pituitary gland may result in a certain type of dwarfism, characterized by a symmetric failure of skeletal development. Such individuals appeared extremely immature initially, but later took on the characteristics of premature aging. Their mentality and sexual development appeared to be normal, but there was usually amenorrhea in the female and azoospermia in the male. There was delayed closure of the epiphyses. X-ray photographs of the sella turcica appeared to be normal except when the causative process was an expanding tumor.

According to Friedgood (1946) hypophyseal dwarfism is a chronic endocrine or neuroendocrine disorder which is generally characterized by adenohypophyseal pathology during the period of somatic development. It may be recognized clinically by a well-proportioned diminutive infantile stature and a correspondingly small head with child-like facial

features, that acquires an oldish expression comparatively early. Union of the epiphyses is delayed markedly or never occurs; however, closure may occur in those hypophyseal dwarfs who, in rare instances, mature sexually. In this type of hypophyseal infantilism,there is a markedly reduced or absence of urinary excretion of neutral 17-ketosteroids and urinary gonadotropin, abnormal sensitivity to injections of insulin,and an increased tolerance for carbohydrates. Friedgood says that it is particularly difficult to distinguish between this type of dwarfism and that which appears to be due to a genetic modification of growth based on germinal defects which he terms "primordial" dwarfism.

According to this author, these primordial dwarfs are of normal intelligence. They are abnormally small at birth, and although their rate of growth remains inhibited, the epiphyses unite at the usual time. They mature sexually at the expected time,and many are able to produce normal offspring. However, there are no autopsy data on primordial dwarfs and only few recorded data on infantilistic dwarfs. In the latter, the adenohypophysis was affected in some way in each instance. The most common disorder is a tumorous growth which destroys or causes pressure atrophy of the gland. Friedgood (1946) compares the primordial and hypophyseal as follows: The face of the primordial dwarf is broad and flat, the head is relatively large, the nose is small and uptilted, and the upper jaw is relatively short. The hypophyseal dwarfs are ordinarily of good intelligence but have the appearance of children with small heads and childish features which, with age, acquire an incongruously wizened expression. The lack of somatic development in these hypophyseal dwarfs is almost universally associated with retarded maturation and growth of the sexual apparatus. However, normal growth of the external

genitalia, spermatozoal maturation,and the development of secondary sexual characteristics occur occasionally in these individuals. In this case they show little beyond the effects of a deficiency of the growth regulating hormone. The epiphyses unite at the time of sexual maturity in dwarfs of the latter type but remain ununited indefinitely in the infantilistic group. Roentgenograms of the skull of the hypophyseal dwarf disclosed pathognomic evidence of adenohyphyseal somatotropic insufficiency. These dwarfs, however, lack uniformity, and the disorder might occur at any age beginning shortly after birth. Many of them ceased to grow entirely in childhood or youth, but others continued to grow at a slow rate into the third or fourth decade, as long as the epiphyses remained ununited.

Friedgood said that it was tempting to consider that the congenitally dwarfed mice of Smith and MacDowell (1931), whose hypophyses were lacking in acidophilic cells, were akin to the primordial variety of human dwarfs.

According to Friedgood (1946), the differentiation of the hypophyseal dwarfism from cretinism is relatively simple. The facial expressions are different. The hypothyroid individual derives its characteristic cretinoid appearance from the position of the horizontally placed slit-like eyes and the depression at the root of the nose, which is due to the delay in development of the nuclei of ossification of the vomer. There is also facial expression and behavioral evidence of retarded mental development. The hypophyseal dwarf, on the other hand, retains a childish facial expression and may be retarded physiologically but not mentally. In general, the dwarfed skeleton retains the child-like body proportions in both disorders; however, the delay in the closure of the

epiphyses and retardation in the time of appearance and development of the various centers of ossification are constant features of hypothyroid dwarfism, which can be determined conveniently by X-ray examination. The extent of the delay in these processes of bone development and growth usually is less in hypophyseal dwarfism than in hypothyroidism; however, the difference is quantitative rather than qualitative and thus is of little use as a diagnostic tool.

He stated that the hematopoietic system suffers seriously in hypothyroidism. The hemoglobin is reduced relatively more than the erythrocytes. In hypophyseal dwarfism, the total erythocyte count is ordinarily within normal limits, but the hemoglobin may be somewhat reduced. In both cases there is a well marked relative lymphocytosis and eosinophilia.

He stated further that the rachitic and achondroplasic dwarfs offered no problem in differential diagnoses. X-ray studies of the ends of the long bones, as well as the classical bony deformities of the rachitic individual, left little doubt as to the etiology of this type of somatic maldevelopment. The achondroplasic dwarf was readily recognized by the disproportionate growth of the trunk and limbs. The extremities were short and considerably bowed and twisted. The sexual development of the achondroplasic dwarf was generally quite normal, and the epiphyses unite at the proper time.

Wilkins (1948) stated that cretinism, or congenital hypothyroidism, was the most common endocrine disturbance encountered during the preadolescent period. He also stated that dwarfism with normal sexual development was probably of genetic origin rather than of endocrine origin. He stated also that hypothyroidism at any period of life was

accompanied by physiological evidences of the lack of the thyroid hormone. There were diminished physical and mental activity, diminished cardiac output and poor peripheral circulation leading to a grayish pallor and coolness of the skin, and diminished intestinal activity which led to constipation. Thyroid treatment caused rapid acceleration of bone development when the retardation was due to thyroid deficiency but had little effect in pituitary deficiencies. Other diagnostic points included high serum cholesterol level and a low serum protein-bound iodine level. A quick diagnosis could be made in children by studying the uptake of radioactive iodine, using a Geiger counter over the neck.

Experimental Studies With Other Animals

Perhaps the most interesting study of dwarfism in laboratory animals was that of Smith and MacDowell (1930, 1931). Snell (1929) reported that he had discovered a recessive type of dwarfism in 1922 in the stock of black silver mice given to him by Dr. L. C. Dunn. Dr. Dunn had obtained these mice in England. The mice appeared to be normal until about weaning time but grew very little after this, attaining only about one-fourth the weight of their normal sibs. These dwarfs were healthy but sterile. Smith and MacDowell studied the endocrine system of these dwarfs and concluded that the primary causal factor, along with the associated disabilities, was a deficiency of the anterior pituitary. These endocrine disabilities resembled those displayed by hypophysectomized rats and could be corrected by fresh pituitary implants. They found a complete absence of eosinophils in the anterior lobe and were unable to demonstrate the presence of the growth-stimulating factor by assay procedures.

The thyroids, gonads, and adrenals were much reduced in size. Fresh pituitary implants brought these glands to normal size, and the animals became fertile, but the pituitary remained in the same defective state.

Even though the development of the gonads appeared to be delayed and these animals were sterile, assays for gonadotropic hormones of the anterior pituitaries of these dwarfs showed them to contain excessive amounts. This indicated that something was wrong with the release mechanism. Therefore, they concluded that this type of dwarfism was hereditary and due directly to a hypofunction of the adenohypophysis.

King (1950) reported having selected some dwarf mice from MacArthur's small race that he called "runts". These "runts" were homozygous for a pair of recessive genes which he termed "pygmy". Apparently they were different from Snell's dwarf mice but they too were sterile and showed underdevelopment of the reproductive system.

Hughes (1944) was able to produce cretinism in rats by injecting them daily from birth with thiouracil. These effects were thought to be brought about by an inhibition of thyroid activity. The condition became permanent following several weeks of injections.

Salmon (1938) produced cretinism in newborn rats by thyroparathyroidectomy. These animals were retarded in growth and had lower body temperatures, sluggish reflexes, awkward muscular movements, persistence of infantile skull proportions, and greatly retarded skeletal development.

Dye and Maughan (1929) reported the results of a study of the effects of thyroidectomy on the growth and development of young puppies. By the second week after thyroidectomy, growth and developmental disturbances could be seen. There was a rapid loss of weight within 3 to 6 weeks

followed by noticeable modifications in general body form. The muzzle became short and broad, the head short and wide (brachycephalic), and the eyes wide apart. The animals became stunted, pot-bellied, humped back, and broad-shouldered. The limbs were farther apart and the feet and legs relatively thicker, broader, and heavier in proportion to their length. At the time they were killed the thyroidectomized dogs weighed 75.7% of the weight of their normal litter mates. Isolated tissues showed a diminution in rate of metabolism of from 22 to 50 per cent as measured by oxygen consumption. There was a diminution of growth in length of all long bones with the most pronounced inhibition of growth of the epiphyseal cartilages, which were less completely ossified in the thyroidless animals.

Later Dye and Kinder (1934) reported the effects of thyroidectomy on skull shape. Removal of the thyroids in young puppies caused retardation of the ossification of cartilage and bone and delayed ankylosis of the sutures. By a restriction of the development of the basal bones the direction of growth was altered producing brachycephaly with a relatively narrow and short skull base. There were a depression of the root of the nose, shortened superior and inferior maxillary bones, saddling of the root of the nose, and a characteristic hypochondroplastic skeletal stunting generally. The skulls of these cretin puppies were relatively shorter, wider, and more vaulted than those of normal puppies. They stated that the possible involvement of the pituitary could not be overlooked, but they made no mention of a study of these pituitaries.

Stockard (1941) made observations on the genetic, developmental, anatomical, and physiological characteristics of several highly modified breeds of dogs, bred selectively over innumerable generations in order

to perpetuate for dog fanciers reproducible types of localized skeletal deformities and generalized disorders of growth. Many of these breeds were characterized by peculiarities of type and dislocations of form and growth, which closely resembled the pathological conditions of achondroplasia, giantism, acromegaly, and hypophyseal dwarfism in human families. A study of the development and adult condition of the Bulldog's skull, the Bassethound's fore and hind limbs, and the entire skeletal system of the dwarf Pekingese led him to believe that these skeletal structures were similar to those of the achondroplastic dwarf. Stockard noted that the physical form and type of individual could be correlated with the histological pattern and cellular nature of the adenohypophysis.

By making certain crosses and growing out F2 generations, Stockard was able to produce acromegalic conditions and dwarfism, as well as achondroplastic dwarfing in some parts and acromegalic overgrowth in other parts of the skeleton of the same individual. He was able to associate these opposite types of growth response with similar histological derangements of the adenohypophysis. He concluded from these studies that the growth response of certain parts of the skeleton to an altered adenohypophyseal secretion depended primarily on the genetic constitution of the tissues, and that the skeletal structure, physiological function, and behavior of an organism were intimately correlated products of an hereditorial genetic background. He believed that these factors affect one another under the influence of an internal chemical environment, the composition of which is regulated and controlled by the endocrine glands. His observations also indicated that the structural pattern and functional activities of the endocrine glands were inherited

characteristics and that a highly significant correlation existed between the inheritance of skeletal deformities and the occurrence of defective development of the adenohypophysis.

Simpson *et al* (1950) have presented some outstanding work on the hormonal influence on skeletal growth in rats, especially as it is influenced by secretions of the endocrine organs. They started off by saying that skeletal growth was measured by an increase in size, particularly an increase in length of the axial and appendicular skeleton, whereas differentiation or maturation was measured by the establishment of ossification centers and their subsequent fusion. Since dwarfism results from removal of the pituitary, their attention was immediately focused on the role of the pituitary hormones and their target organs. They found that hypophysectomy of young animals caused cessation of growth almost immediately, both in length and in weight. The epiphyseal plates became sealed from the marrow by a lamina of bone and resembled that of the senescent normal rat.

These workers found that thyroidectomy resembled hypophysectomy in young rats in that growth is markedly retarded; however, the epiphyseal cartilage did not become sealed off by a boney plate,even after long postoperative intervals. Some proliferative activity persisted,and some erosion continued. The cartilage plates were not reduced in width but were even wider than normal animals at 56 days of age. The pituitary became badly deranged following thyroidectomy. The alpha cells, which are believed to produce the growth hormone, were much decreased in number. If both the thyroid and the pituitary glands were removed,the bone resembled that of thyroidectomy alone in that the cartilage plates were not sealed,and the skeletal age was the same.

These workers believed that growth and differentiation of the skeleton were largely under the control of the growth hormone and thyroxin; however, it could be greatly modified by dietary and environmental factors. They reported that thyroid hormone injected into normal rats caused no increase in body length, but in combination with growth hormone it accelerated the effects of the growth hormone. Thyroid hormone injected into hypophysectomized rats caused barely detectable growth, but it stimulated maturation of the bone, reduced the width of the epiphyseal plate, and led to an increased bone age. However, in combination with growth hormone, bone growth and maturation occurred.

They found that hormone injections into thyroidectomized rats led to spectacular resumption of growth along with maturation of the osseous system leading to a normal rate of increment of skeletal age. Repair of the pituitary also occurs. They concluded that it might be assumed that the increase in size was brought on by the resumption of growth hormone secretion.

Since the growth hormone elicited growth in hypophysectomized, thyroidectomized, hypophysectomized-thyroidectomized, adrenalectomized, and gonadectomized rats, and various combinations of these, Simpson et al (1950) concluded that its effects were directly on the body tissues instead of through other endocrine organs. They stated also that the response of different bones of normal rats to growth hormone was conditioned by the physiology of the individual bone and that growth hormone did not accelerate epiphyseal closure any more than it prevents closure at the normal time.

They found that ACTH caused retardation of body growth, both chondrogenesis and osteogenesis, with narrowing of the epiphyseal plate.

This effect was through the adrenal cortex. However, in hypophysectomized rats ACTH did not further decrease chondrogenesis and osteogenesis but inhibited the effects of growth hormone.

They found that testosterone had no effect on growth in the absence of the pituitary, and there was no significant stimulation of bone growth. They concluded that apparently the effect was due either to a stimulation of the pituitary or a synergistic action with growth hormone. They found that estrogen inhibited growth in rats through its action on the pituitary

Moore (1950) reviewed the literature on the role of the endocrine organs in fetal development. He concluded that (1) probably in all cases there is a gradual development of secretion within the gland, as well as a gradual development of the sensitivity of the target organ to the hormone; (2) most of the experimental evidence with mammals, although not always yielding comparable results, do,in the aggregate,suggest that some influence issues from the pituitary during embryological development which plays a role in normal tissue differentiation and morphogenesis; (3) the influence of the pituitary hormones during embryological development has been unmistakably pointed out in amphibians and strongly indicated in birds; (4) the presence of an active substance in the gland does not assure that this substance is being discharged into the organism or that it exerts any effect upon development; and (5) the end organ or tissu must be capable of responding to the hormonal substance before any respons can occur.

Baird et al (1952) stated that it has been generally assumed that the genes governing the expression of economic characters in animals do so by controlling the rate at which the glands concerned with growth produce and liberate their hormones. They were unable to find reports

of such studies in the literature, however, and went about making a study of the growth hormone content of the pituitaries of fast and slow growing lines of swine. They started out with a line which had an average weight at 180 days of age of 141.8 pounds. From these foundation animals they selected in both directions for several generations. At the end of nine generations the rapid line had increased to 171.8 pounds but the slow line had decreased in 8 generations to 110 pounds. The daily gain in the rapid line on a 72-day feeding trial was .94 pounds but that of the slow line was .31 pounds.

Animals from each of these lines were killed at 56, 75, 115, and 154 days of age, and at maturity, and their pituitaries were assayed for growth hormone content. At all ages and weights a unit of anterior pituitary powder from the rapid line contained more growth hormone than the same unit from the slow growing line. The differences were significant, with the exception of the 56-day glands, at all ages including maturity. The growth hormone potency per unit of anterior pituitary tissue remained quite constant with age, even at maturity. They concluded that since the ratio of anterior pituitary weight to body weight generally decreases with age it can be postulated that growth occurs only so long as the pituitary is able to maintain an adequate concentration of growth hormones in the body as a whole. Increasing the body weight leads to a dilution of the circulating hormone until growth stasis results at maturity because the growth hormone liberated is only able to maintain size without further growth.

They stated that the differences in growth rate between the two lines were shown to be due to differences in growth hormone secretion that in turn were due to differences in genetic constitution of the individual animals.

There is a dominant autosomal gene in mice which produces a yellow coat color and for this reason is commonly called the "yellow" gene. In the homozygous state this gene is lethal, but in the heterozygous state it greatly decreases the food required per pound of gain after about 40 days of age and at the same time greatly increases the proportion of fatty tissue to total gain. These yellow mice exceed their black littermates greatly in gain with an only moderate increase in food consumption. Dickerson and Gowan (1947) showed that this lowered food requirement per gram of gain and increased fat deposition was accomplished by increased appetite and reduced energy expended in body work, especially in activity. These authors cited the work of Weitze (1940), which indicated that the action of the yellow gene was hormonal, involving altered carbohydrate metabolism. They stated that there was evidence that the action of the "yellow" gene was similar to that of genes affecting fat deposition in animals generally.

NATURE, SCOPE AND RESULTS OF EXPERIMENTAL STUDIES

Since most of the evidence points to an endocrine malfunction in cases of dwarfism in many species and since the literature strongly implicates the pituitary in dwarfism in beef cattle, a study was undertaken to determine whether there was a deficiency of one or more of the anterior pituitary hormones in dwarf beef cattle.

The pituitary is an organ of complex structure and extraordinarily complex function. Into it is compressed per unit of volume substances probably of more actual and potential activity than are found in a similar amount of tissue anywhere else in the body. Its actions are both direct and indirect for it exercises a dominating control over the activities of nearly all of the other endocrine glands of the body, increasing or decreasing their functioning as needed for the control of the body processes. Its function results largely from the formation of many hormones by the pituitary itself and the control of hormone formation by the other endocrine organs. Therefore, it is obvious that pathological changes in the pituitary might cause marked and complex effects in the structure and function of many parts of the body.

The major part of this study has been devoted to assaying for the thyrotropic, growth, gonadotropic, and adenocorticotropic hormones of the anterior pituitary. The procedures used, data and results obtained, and a brief discussion of each series of assays is presented under the particular hormone involved. The activity of the thyroid and parathyroid glands was determined from blood analyses. An effort was made to correlate the weights of the trimmed pituitaries and the glandular powder

with the live weight of the animal.

Pituitary glands were collected from approximately 75 dwarf calves of the Hereford and Angus breeds and a somewhat smaller number from normal calves. These glands were trimmed, weighed on a precision balance, and immediately placed in acetone and stored in a refrigerator until ready for use. Just prior to the beginning of an assay the glands were removed from the acetone, the connective tissue capsule was removed and all of the glandular material was macerated in a small mortar until a fine powder was obtained. Particular care was taken to remove all extraneous material which failed to powder. The powder was then carefully weighed, suspended in the desired amount of neutral physiological saline solution,and stored in the refrigerator between injections. This procedure was used throughout the entire series of assay for all of the hormones studied.

In several instances the same assay animals were used to measure the response to two or more hormones simultaneously.

THYROTROPIC HORMONE ASSAYS

The control of thyroid activity is by the thyroid-stimulating hormone produced by the anterior pituitary. There is a reciprocal relationship between these organs since the level of circulating thyroxin in the blood controls the production and/or release of thyrotropin by the pituitary.

Cretinism, a form of dwarfism, in humans has long been associated with hypothyroidism. Cretinism in laboratory and domestic animals has been produced experimentally by ablation of the thyroids or by feeding or injecting substances which prevent the normal production and release of either thyroxin or thyrotropin. The similarities between cretinism in humans and experimental cretinism in animals and those characteristics expressed in dwarf beef cattle have led certain workers to believe that dwarfism in cattle is the result of a hypothyroid condition. Carroll et al (1951) of the California Station reported finding a gross deficiency of thyrotropin in the pituitaries of dwarf calves and attributed the causal factor of dwarfism to this deficiency.

Many workers have reported finding pituitaries and thyroids considerably smaller in dwarf than in normal cattle, indicating a hypothyroid condition (Craft and Orr, 1924; Carroll et al, 1951; Gregory et al, 1953; Lindley, 1951). Histological examinations of these thyroids have failed to show any abnormalities, however (Johnson et al, 1950; Gregory et al, 1953; Lindley, 1951).

Other workers (Reece and Turner, 1937; Adams, 1946; Bates et al,

1935; Baird et al, 1952) have shown that the thyrotropic hormone content of the pituitary varies greatly between species and even between individuals within the same species, depending upon age, sex, stage of pregnancy or lactation, and genetic constitution.

A very active thyroid gland is generally associated with a high content of TSH in the anterior pituitary of normal animals. Adams (1946) concluded that assays yield dependable data as to the amount of hormone present in the gland but that they tell little or nothing about the amoun being released. Thus the activity of the thyroid itself or the amount of thyroxin or TSH in the blood and urine is a better indication of the amount of TSH being released. There appears to be a delicately balanced relationship between the amount of thyroxin produced and stored or released by the thyroid and the amount of TSH produced and stored or released by the anterior pituitary.

Long et al (1952) and O'Neal and Heinbecker (1953) state that protein-bound iodine appears to be a useful test to determine thyroid activity since it measures the level of iodinated protein in the serum which, under normal conditions of diet, is made up primarily of thyroxin and its related substances. They found highly significant differences between breeds of cattle and dogs and attributed these differences to differences in heredity. Kunkel et al (1953) at the Texas Station have found a distinct relationship between the level of serum protein-bound iodine and rate and efficiency of gain in beef cattle. Their data indicated an optimum level of between 4.0 and 4.9 micrograms per 100 ml of serum with either higher or lower levels associated with a slower rate of gain. They also observed a highly significant correlation between the PBI level and the rate of metabolism in male beef calves.

Studies by Nandler et al (1954) and Hoffman and Shoffner (1950) have shown that there is a positive relationship between thyroid weight and its functional level.

Procedure

The assay procedure used for thyrotropin was essentially that of Bergman and Turner (1939). In brief, day-old White Leghorn cockerels were injected daily subcutaneously for 4 days and sacrificed the day following the last injection. The thyroids were removed and trimmed with the aid of a binocular loupe, blotted lightly, and immediately weighed on precision balances.

All assays were conducted on a per gland basis in order to remove the gland-to-gland variation among calves. These dwarf and normal calf glands were comparable as to breed and sex, but because of the impracticability of obtaining dwarf and normal calves of similar ages the normal calves were somewhat older on the average than the dwarfs.

Thyrotropic hormone assay No. 1 was conducted in the summer of 1952 and consisted of two trials. A total of 80 chicks were injected with pituitary powder from 8 dwarf and 7 normal calf glands. Each trial consisted of two levels of injection of pituitary powder, and in each case a saline control group was included.

Assay No. 2 included 173 chicks, 6 dwarf glands, 4 normal calf glands, and 2 saline control groups. The pituitary suspension from each gland was injected into 15 chicks on three levels. Five chicks each received .1, .5, and 1.0 mg of pituitary powder daily. The .1 and .5 mg levels were in .05 ml suspensions, but the 1.0 mg was in a .10 ml suspension. One group of controls received .05 ml of saline daily, but the other control group received .10 ml of saline daily. Since there was no

difference between the two control groups, these data were pooled.

Assay No. 3 was conducted just as No. 2 with the exception that the .1 mg level was omitted since there was no significant difference between this level and the controls in the previous assay. Only two dwarf and two normal calf glands were used in this assay. They were all from female Hereford calves.

Assay No. 4 began with 144 day-old White Leghorn-Black Australorp crossbred cockerels divided into 24 groups of 6 chicks each. Ten groups were each injected with a suspension of 1.0 mg of dwarf calf pituitary powder twice daily, 5 groups starting the afternoon of hatching and the other 5 groups starting the following day. Injections were made twice daily because it was desired to get a measure of gonadotropic potency on these same chicks. Ten groups receiving normal calf pituitary powder, 2 groups receiving saline only, and 2 groups receiving a purified preparation of thyrotropin were similarly treated. This procedure was used in order to eliminate the need of autopsying so many birds on one day. It was planned that one half of the groups of each treatment would be sacrificed on the fifth day and the other half on the sixth day. However, the heat went off in the brooder the last two nights of the test, dropping the environmental temperature below the critical level for the baby chick and causing hypertrophy of the thyroids of all groups. Since the thyroid weights of the first 70 chicks killed were double those of previous assays presumably because the cold stimulus had overshadowed that of the injections, the remaining groups were injected twice daily for two additional days with the dosage level doubled. They were autopsied on the seventh day and handled just as in previous assays. All thyroids were removed by one person in assays No. 3 and 4,

whereas two people removed glands in the other assays.

In all assays the chicks and treatments were allotted completely at random to the brooders. Both Hereford and Angus glands were used in all assays except No. 3. Thyroid weights are reported both on an absolute and on a percentage of body weight basis. All analyses except assays No. 1 and 2 are for the milligram per cent of body weight values.

Blood samples were taken from groups of dwarf and normal calves comparable as to age, breed, and sex and analyzed for the serum protein-bound-iodine content. The weights of the thyroid glands were also compared for dwarf and normal calves.

Data and Results

A summary of all of the data obtained from this series of assays is given in Table I. A more detailed breakdown of these findings is given in Tables X through XIII of the appendix.

Assay No. 1 was a preliminary trial in an effort to establish the proper level of injections. These injections were intramuscular, whereas in the remaining assays the chicks were given subcutaneous injections. Analysis of variance failed to show any significant differences in the response to dwarf and normal calf glands. However, the thyroids from the pituitary-injected groups were significantly heavier than those from the control groups. In Trial I the mean thyroid weights were 3.90 mgs for the saline controls, 5.5 and 5.9 for the two levels of dwarf pituitary injections, and 6.2 and 5.7 mgs for the two levels of normal calf pituitary injections.

It can be seen that as the level of injection increased in Assay No. 2 there was an increase in the weight of the thyroids. These differences are

TABLE I THYROTROPIC HORMONE ASSAYS USING DAY-OLD CHICKS

	Treatment	Total Mat. per Chick	No. of Glands	No. of Chicks	Final Weight	Thyroid Mgs	Wts. Mgs%
A	Assay No. 1 (Summer, 1952)						
	Trial 1						
	Saline	.4 ml	0	21	62	3.9	6.4
	Dwarf Calf Pit.	4.0 mg	5	23	59	5.5	9.3
		8.0 mg	3	15	58	5.9	10.2
	Normal Calf Pit.	4.0 mg	4	20	59	6.2	10.5
		8.0 mg	2	8	54	5.7	10.5
	Trial 2						
	Saline	.4 ml	0	6	92	4.7	5.1
	Dwarf Calf Pit.	1.32 mg	1	4	87	6.2	7.1
		2.68	1	3	86	5.8	6.7
	Normal Calf Pit.	1.32	1	4	94	7.5	8.0
		2.68	1	3	100	7.4	7.4
B	Assay No. 2 (Spring, 1953)						
	Dwarf Calf Pit.	.4 mg	6	30	74.4	4.4	6.0
		2.0 mg	6	30	71.2	5.7	8.1
		4.0 mg	6	29	71.6	5.9	8.2
	Normal Calf Pit.	.4 mg	4	20	74.2	5.5	7.5
		2.0 mg	4	20	78.3	6.0	7.7
		4.0 mg	4	19	73.6	7.4	10.1
	Saline Controls	Saline	0	23	74.0	4.4	6.0
C	Assay No. 3 (Fall, 1953)						
	Dwarf Calf Pit.	2.0 mg	2	17	54.2	5.4	10.1
		4.0	2	16	55.6	6.0	11.0
	Normal Calf Pit.	2.0 mg	2	20	60.0	6.1	10.2
		4.0	2	19	61.5	7.0	11.4
	Saline Controls	Saline	0	19	57.7	5.1	8.8
	Thyrotropin	0.8 mg	0	10	57.0	10.5	23.8
D	Assay No. 4A (Spring, 1954)						
	Dwarf Calf Pit.	6.0 mg	5	29	48.3	5.7	12.1
	Normal Calf Pit.	6.0 mg	5	26	49.9	5.8	12.1
	Saline Controls	Saline	0	10	51.5	6.7	13.6
	Thyrotropin	1.2 mg	0	5	51.7	10.1	19.4
E	Assay No. 4B (Spring, 1954)						
	Dwarf Calf Pit.	13.0 mg	5	28	60.9	5.1	8.6
	Normal Calf Pit.	13.0 mg	5	27	61.0	5.8	9.7
	Saline Controls	Saline	0	9	76.8	5.3	6.9
	Thyrotropin	1.2 mg	0	10	64.3	10.8	18.8

highly significant. There was no difference between the controls and the low level of dwarf calf gland injections. The low level of the normal calf gland injected group is slightly higher than the controls,but this difference is not significant. The other levels were significantly higher than the controls, indicating a satisfactory response. The mean chick thyroid weights and their standard errors were 4.4 ±.40 for the control group, 4.4 ±.24, 5.7 ±.45 and 5.9 ±.36 for the three levels of dwarf pituitary injections, and 5.5 ±.54, 6.0 ±.35 and 7.4 ±.45 for the three levels of normal calf pituitary injections. The difference in thyroid weight between the groups injected with dwarf and normal calf glands approached significance (P=.07). When the gland weights were converted to a percentage of body weight, however, this difference was reduced.

Assay No. 3 included an additional group of 10 chicks that were injected with .2 mg of a purified preparation of thyrotropin. A summary of these results is shown in Section C of Table I. The mean thyroid weights and standard errors on a milligrams per cent of body weight basis were 8.8± .63 for the saline control group, 10.1 ±.68 and 11.0 ±.68 for the dwarf pituitary groups, 10.2 ±.68 and 11.4 ±.68 for the normal calf pituitary groups, and 23.8± 2.2 for the thyrotropin injected group.

Although there was a slight increase in thyroid weights with an increase in the level of injections of pituitary suspension, this difference was not significant. Neither was there any difference in the thyroid weights of the chicks injected with dwarf and normal calf pituitary powder. The difference between the pituitary injected groups and the control group was significant at the .05 level, but the difference between the thyrotropin group and pituitary injected groups was significant at the .01 level of probability.

As a result of the tremendous variation in thyroid weights within each treatment group in the previous assays, it was decided to use crossbred chicks in the fourth assay with the idea of obtaining more uniformity within groups treated alike. Consequently, 160 White Leghorn-Black Australorp crossbred cockerels were obtained. Since it was desirable to check the response to gonadotropins present in the glandular powder on these same chicks, injections were administered twice daily. A summary of these data is presented in Section E of Table I.

The mean thyroid weights on a milligrams per cent of body weight basis were 6.9±.28, 8.6±.73, 9.7±.81, and 18.8±1.4 for the saline control, dwarf calf glands, normal calf glands, and thyrotropin-injected groups, respectively. Analysis of variance showed that there was no significant difference between the dwarf and normal calf pituitary-injected groups. The difference between the saline controls and the pituitary-injected groups was slightly below the .05 level, and the difference between the thyrotropin and the pituitary-injected groups was significant at the .01 level of probability.

Analysis of blood samples from groups of 16 dwarf and 5 normal calves gave mean serum protein-bound iodine values of 5.59±.29 and 6.28±.12, respectively. The PBI values for the dams of these calves were 4.28±.19 and 4.00±.41 for the "carrier" and normal cows, respectively. These differences were not significant.

Discussion

The results of this investigation are not in agreement with those of Carroll *et al* (1951) and Gregory *et al* (1953), who found a gross thyrotropic hormone deficiency in the pituitary glands of dwarf beef calves.

In no case did the present data demonstrate a significant difference in thyrotropic potency of dwarf and normal calf glands. However, in no assay were the dwarf glands more potent than the normals and in most cases the mean values were in favor of the normal calves. This difference in favor of the normal calf glands approached significance ($P = .07$) in assay No. 2.

These slight differences in favor of the normal calf glands can probably be accounted for by the fact that, on the average, the normal calves were older than the dwarfs. Reece and Turner (1937) showed that thyrotropic potency increases with age up to 4 to 10 months and decreases thereafter. Since practically all of our normal cattle were within the age range of 4 to 12 months, they should have been at the peak of their thyrotropic potency. Probably not more than one-half of the 20 to 25 dwarf glands used in this series of assays fell within this age range. Careful precaution was taken to balance the sexes, breeds, and, insofar as possible, the ages.

Since the dwarf calves grow at a much slower rate than normal calves and are apparently troubled with metabolic disturbances, it seemed reasonable to suspect some abnormal thyroid function. Blood serum analyses for protein-bound iodine content failed to reveal any significant difference between dwarf and normal calves, however. It was found that on an absolute basis the thyroid glands of dwarf calves are considerably lighter than those of normal calves. However, it is well known that the weight of the thyroids, as a percentage of total body weight, decreases with increased age and weight in normal animals. A comparison of a limited number of glands failed to reveal any significant difference on a percentage of body weight basis between dwarf and normal calves when the animals compared were comparable as to breed, sex, age, and/or weight.

These data indicate that there was no gross deficiency of thyrotropic hormone in the pituitary glands of the dwarf calves used in this study.

GROWTH HORMONE ASSAYS

Abnormal bone growth has been noted in dwarf cattle, in cretins, and in dwarfs of other species. It has been shown that diet, various environmental factors, and a number of hormones influence growth. However, according to Greenspan *et al* (1950) growth hormone is the only substance which will cause rapid and continuous growth in animals.

Smith and MacDowell (1930, 1931) reported results of endocrine studie on a strain of dwarf silver mice in which they found a complete absence of eosinophils in the anterior lobe of the pituitary, and assays failed to demonstrate the presence of any growth hormone within the gland. Dwarfism in beef cattle resembles the conditions described in dwarf mice by Smith and MacDowell in many respects.

Certain types of dwarfism in humans have been shown to be associated with a deficiency of the growth hormone. Excessive secretions of this hormone produce a condition known as acromegaly in adults, which is characterized by an overgrowth of the bones of the face, hands, and feet. If this type of pituitary defect occurs prior to maturity, giantism results before the closure of the epiphyseal cartilages limits the growth of the long bones.

Campbell *et al* (1953) have shown that injections of growth hormone into intact dogs produced(1) a tremendous increase in sedimentation rate of the blood cells, (2) considerable hypercalcemia and glycosuria,which in very large doses may lead to permanent diabetes, (3) a leucocytosis, due to an increase in neutrophil granulocytes and stab cells, and (4) other abnormalities which need not concern us here.

It has been reported that dwarfism in other species of animals might result from many causes (Friedgood, 1946; Smith and MacDowell, 1930, 1931; Wilkins, 1948), including a deficiency of the growth hormone, and the dwarf calf has been shown to be abnormal in skeletal development. Therefore, since growth hormone has been shown to have a direct influence on bone growth (Simpson et al, 1950), it seemed reasonable to assume that dwarfism in beef cattle might be the result of an insufficient amount of growth hormone.

Procedure

In the spring of 1953 experimental studies were initiated to determine whether there was a growth hormone deficiency in the pituitaries of dwarf beef calves. Three separate studies have been completed. Greenspan et al (1950) reviewed the procedures of assaying for the growth hormone and recommended the following well-established procedures: (1) the increase in body weight of normal plateaued rats, (2) the increase in body weight of hypophysectomized rats, (3) the increase in body weight of dwarf mice, (4) the increase in tail length of hypophysectomized rats, and (5) the tibia test. All of these procedures were used in this series of assays except number 3. In addition, the sedimentation rate of the blood cells, blood sugar content, and phosphatase activity have been determined for dwarf and normal calves and for the assay animals which were injected with pituitary material from them.

In all assays the pituitary injections consisted of acetone-dried powder of the entire gland suspended in neutral physiological saline. In all experiments the assay animals were allotted at random to individual cages.

In the first experiment the plateaued female albino rat was the assay animal. The procedure was essentially that of Marx et al (1942). In brief, adult female rats of the Sprague-Dawley strain, 5 to 6 months old, weighing 220 to 280 grams, in whom growth stasis had been demonstrated by their failure to gain more than 10 grams in the 20 days prior to the injection period, were used. All rats were fed the stock ration, which consisted of 56% yellow corn meal, 20% soybean oil meal, 20% whole dried milk, 2% alfalfa leaf meal, 1% Brewer's dried yeast, .25% cod liver oil, .5% Ca CO_3, and .5% Na Cl. The diet and environmental conditions were not changed during the test. The animals were injected intraperitoneally daily on three different levels for a period of 15 days. The high level group was continued for an additional 7 days.

The low level group received 1 mg of the pituitary material daily per rat for 7 days followed by injections of 4 mgs daily for 9 days. They received 43 mgs during a 16-day period. The medium level group received 2 mgs daily for 7 days and 8 mgs daily for 9 days, making a total of 86 mg during a 16-day injection period. The high level group received 4 mgs daily for 7 days and 12 mgs daily for 14 days. They received 196 mgs of acetone-dried powder during the 21-day injection period. Injections of the low and medium level groups were discontinued on the 16th day so that the limited amount of dwarf pituitary powder could be used at the high level. A total of 26 dwarf and 17 normal calf glands were used in this assay. The measures of response included (1) the increase in body weight and (2) the increase in tail length.

In the second and third experiments hypophysectomized immature female rats of the Sprague-Dawley strain were used. These rats were hypophysectomized on the 26-28th day, and the injections started 14 days

postoperatively. In addition to the stock ration, these rats were fed fresh oranges, carrots, whole milk, bread, and canned dog food daily. The diet and room conditions were similar for all groups. The measures of growth response in the second trial included: (1) increase in body weight, (2) increase in tail length, (3) increase in width of the epiphyseal cartilage of the tibia, (4) blood sugar concentration, and (5) sedimentation rate of the blood cells. The injection period for this trial was 14 days, and the animals were sacrificed on the following day.

Because the mortality rate was quite high in the second trial, a third experiment was designed for a shorter injection period (5 days); the primary measure of growth response in this assay was the increase in width of the epiphyseal cartilage of the tibia, commonly referred to as the tibia test. This test was based on the bioassay method of Evans et al (1943) and standardized by Greenspan et al (1949). Briefly, it consists of removing the right tibia at autopsy by dissecting it free from the soft tissues and splitting the proximal end in the mid-sagittal plane with a sharp razor. The bone halves are fixed in 10% neutral formalin until ready for staining. Prior to staining they are washed in water for one-half hour, immersed in acetone for at least an hour, and then washed in water again for one-half hour. They are then placed in freshly prepared 2% silver nitrate for 2 minutes, rinsed in water, and exposed to a strong light while under water until the calcified portions appear dark brown. They are then immersed in 10% sodium thiosulphate for 25 to 30 seconds and washed in running water for another half hour. The width of the uncalcified epiphyseal cartilage is measured under the low power of the microscope, using a micrometer eyepiece calibrated with a stage micrometer so that the results may be expressed in

micra. A minimum of 5 to 8 readings were taken and the results averaged. While not being measured, the tibiae were stored in 80% ethynol. Blood samples were taken from these animals while anesthetized just prior to autopsy, and the sedimentation rate was determined. Random samples from each group were also analyzed for blood sugar and phosphatase activity. Because of the very short (5 days) injection period, changes in body weight and tail length were not thought to be appropriate measures of response to the treatments.

Data and Results

A summary of the data from the plateaued rat assay is given in Table II. It will be noted that the injections of pituitary suspensions were at three levels. However, the analysis of variance failed to show any significant differences due to levels. It was surprising to find that rats receiving the pituitary suspension from the dwarf calves showed a greater response to growth hormone than those receiving pituitary suspension from normal calves. The average body weight increase for the dwarf injected group was 16.6 grams, whereas the group injected with normal calf pituitary tissue gained 11.3 grams. This difference was significant at the .05 level of probability. The increase in length of tail was also in favor of the dwarf group,but this difference was not statistically significant. Another point of interest was that gains decreased as the dosage increased within the dwarf group. There was practically no increase in the average rat weight during the first week of injections in either the dwarf or normal groups, whereas the purified growth hormone group gained an average of 18 grams per rat. All groups gained slowly during the second week with only the high level (12 mgs daily) normal

TABLE II - PLATEAUED RAT ASSAY FOR GROWTH HORMONE

Treatment	Glands Used	No. of Rats	Level of Injection	Body Wt. Gain 14 days	Body Wt. Gain 21 days	Increase in Tail Length 14 days	Increase in Tail Length 21 days
		9	1	7.0	19.7	2.33	3.11
Dwarf calf pituitaries		9	2	9.3	17.8	2.78	3.33
		9	3	5.1	12.4	2.89	3.11
	13M, 13F	27	av.	7.2	16.6±1.5	2.67	3.19±.19[1]
		9	1	6.1	13.9	2.22	2.44
Normal calf pituitaries		9	2	5.9	7.0	2.11	2.44
		9	3	7.4	12.9	3.67	4.35
	9 M, 8 F	27	av.	6.5	11.3±.6	2.67	3.07±.29
Saline Controls	0	9	.4ml	3.8	5.6±2.9	1.56	2.89±.36
G. H. Controls	0	9	.5mg	32.6	44.2±2.1	3.56	4.00±.41

[1] Refers to the standard error of the mean

group gaining an average of more than one gram daily. Due to the fact that the supply of pituitary powder from dwarf calves was becoming exhausted, only the high level groups continued to receive pituitary injections after the sixteenth day. The other two groups, although not injected beyond the sixteenth day, were kept on feed for the 21 days of the assay. On the 22nd day all rats were weighed and their tails were measured. The tail measurements were an average of three separate measurements with a calibrated plastic tube of decreasing diameter into which the tail was inserted. By using this technique, the tail measurements were highly repeatable. All three measurements on one rat were identical in many instances,and very seldom did a measurement vary more than one millimeter from the average of the three measurements taken on each individual.

Even though the injections were discontinued on the sixteenth day for the low and medium level groups, the greatest gains were made during the third week with the exception of the medium level group on normal calf pituitary. Increases in body weight and tail length were considerably greater in the dwarf pituitary injected group than in the group injected with normal calf pituitary except at the high level of injection. The saline control group gained significantly less weight than the pituitary injected groups. The group receiving a purified growth hormone preparation gained more weight and had a greater increase in tail length than the pituitary injected groups. These differences were statistically significant.

The results of the second experiment are shown in Table IIIA. Here again the dwarf glands gave a greater growth response in hypophysectomized rats than the normal glands. The mean body weight gains and

TABLE III – HYPOPHYSECTONIZED RAT ASSAY FOR GROWTH HORMONE

Treatment	No. of Glands Used	Total Material Per Rat	Final Wt.	Weight Change (gms)	Increase in Tail Length (mm)	Width of Epiphyseal Cartilage	Blood Data	
							Sugar	Sed. Rate
A Jan. Assay (14 days)								
Dwarf Calf Pituitary	15	61 mgs	84	18.0 (24)[1]	5.5 ± .8 (24)	149 ± 7.9 (23)	89 (20)	1.86 (21)
Normal Calf Pituitary	10	61 mgs	75	9.7 (11)	3.6 ± .6 (11)	133 ± 8.7 (14)	82 (8)	1.38 (8)
Hypo. Control Rats	0	Saline	55	-5.3 (3)	00[2] (3)	75 ± 6.3 (7)	92 (2)	0.75 (2)
Growth Hormone	0	3.5 mgs	102	35.4 (5)	16.2 ± 1.4 (5)	211 ± 21.4 (6)	108 (5)	6.10 (5)
Normal Rats	0	Saline	142	51.6 (10)	23.1 ± .6 (10)	196 ± 23.6 (6)	118 (10)	1.60 (9)
B March Assay (5 days)								
Dwarf Calf Pituitary	6	30 mgs	72.1	4.4 (15)		147 ± 11.6 (12)	45.1 (5)	2.1 (11)
Normal Calf Pituitary	6	30 mgs	73.2	4.9 (17)		131 ± 9.3 (15)	54.5 (4)	2.1 (15)
Hypo. Control Rats	0	Saline	72.8	3.5 (6)		104 ± 8.5 (6)	——	3.3 (4)
Growth Hormone	0	3.0 mgs	82.8	12.9 (10)		280 ± 8.9 (5)	75.8 (3)	5.2 (5)
Normal Rats	0	Saline	138.4	27.3 (10)		272 ± 18.5 (3)	75.9 (4)	1.4 (10)

[1] The number in parenthesis refers to the number of animals measured.

[2] Insufficient numbers to determine the standard error of the mean.

standard errors during the 14-day injection period were 18±2.2 grams for the rats injected with dwarf glands and 9.7±1.1 grams for those on pituitary from normal calves. This difference is highly significant. The control group lost an average of 5.3±3.0 during this period. All other measurements, including increases in tail length, width of the epiphyseal cartilage of the tibia, blood sugar, and sedimentation rate, were in agreement with this observation. However, they were not statistically significant at the .05 level of probability. There were highly significant differences between the controls and the pituitary injected groups in body weight and tail length changes.

The primary measure of response to growth hormone activity used in the third experiment was the width of the epiphyseal cartilage of the tibia. Blood glucose, sedimentation rate, and phosphatase activity were also determined for a few animals from each group. None of these measures showed a significant difference between the groups receiving pituitary suspensions from dwarf and normal calves. However, the width of the epiphyseal cartilage was slightly greater for the dwarf injected group, being 147±11.6 micra for the dwarfs and 131± 9.3 micra for the normals. Since the difference between the controls and the pituitary-injected groups was not great enough to be significant at the .05 level, perhaps the level of injection was too low for such a short period. Greenspan et al (1949) considered the minimum significant increase in the width of the epiphyseal cartilage to be 30 micra. On the other hand, these rats increased in body weight at about one gram per day, which is a satisfactory rate according to the above references. They stated further that only pituitary growth hormone will stimulate the cartilage above the level of 160 to 190 micra and that the most satisfactory working range of the log

dose curve is approximately 190 to 314 micra. It can be seen in Table IIIB that the groups injected with pituitary suspensions were not within this range but that the non-hypophysectomized rats and the hypophysectomized rats receiving growth hormone fell within this recommended range.

Analysis of blood from groups of dwarf and normal calves was made for glucose level and for phosphatase activity. These means and their standard errors are shown in Table IV below. None of these differences were statistically significant.

TABLE IV - SUMMARY OF BLOOD ANALYSIS FOR GLUCOSE AND PHOSPHATASE

Group	No. of Animals	Glucose in mgs%	Phosphatase B. units/ ml plasma
A			
Dwarf Calves	10	51.84± 4.47	20.73± 2.4
Normal Calves	9	39.47± 5.48	19.82±1.9
B			
Dwarf Calves	13		2.7 ± .24
Normal Calves	5		2.8 ± .31
Carrier Cows	15		6.2 ±1.70
Normal Cows	13		2.9 ± .87

The blood for the analysis shown in Section A of the table was collected in January, 1954, whereas that of Section B was collected in June, 1953. Data on individual animals are shown in Table XVI of the appendix.

The wide variations among animals obtained in these analyses are in line with those obtained by Crookshank et al (1952). These workers obtained values between 1.0 and 2.9 Bodansky units per milliliter of fresh serum for 44 per cent and between 13.0 and 24.9 units for 18 per cent of the cows tested. They did not suggest a normal range of phosphatase activity for beef cattle.

Discussion

The data obtained in this series of assays indicate that there was not a deficiency of growth hormone in the pituitary glands of dwarf beef calves of the Hereford and Angus breeds. On the contrary, there appeared to have been an excess of this hormone in the glands of the dwarf calves. Carroll et al (1951) reported that the growth hormone in the pituitaries of dwarf Hereford calves was highly potent, but they did not state whether or not it was more potent in dwarfs than in normal calves. Whether this difference is real can be determined only by additional research.

It is conceivable that sufficient growth hormone was produced by the pituitary of the dwarf calf, but for some unknown reason it may not have been released into the circulatory system in sufficient quantity to stimulate normal growth.

It is known that hormones are being produced by the pituitary long before they are liberated into the blood stream in effective amounts. Just what causes this release is unknown, but it may be under genic control. If the responsible gene should mutate so that in the homozygous condition it could no longer function in a normal way, it is conceivable that the gland might produce the hormone but not release it in sufficient quantity to maintain normal growth and development. On the other hand, there might be something in the genetic and physiological make-up of the individual which prevented the proper utilization of the hormone or caused its destruction before it could perform its function. In this case the gland might produce the hormone in excessive amounts in an effort to supply the demands of the body. Ershoff (1952) has pointed out that an increase in hormonal potency of a gland may be due to either an increased production or a decreased liberation of the hormone.

GONADOTROPIC HORMONE ASSAYS

Testosterone and small amounts of estrogen have been shown to stimulate growth in animals and in man (Burroughs, 1954; Friedgood, 1946; McCullagh 1948; Marx, 1944). Many writers have associated growth with the production of sex hormones in humans. McCullagh (1948) stated that gonadotropin production by a healthy anterior lobe is difficult to suppress except by the use of estrogens. Sperm counts make an excellent method of assay for pituitary gonadotropic hormone production in man. Where dwarfism and hypogonadism are associated, a pituitary defect can be suspected. Quite frequently boys, who exhibit symptoms of dwarfism and hypogonadism but who have no pituitary tumor and apparently normal quantities of urinary FSH, respond well to treatment with either chorionic gonadotropins or testosterone in general growth as well as sexual maturity.

Wilkins (1948) stated that somatic growth in boys is influenced by androgen, and that in cases of precocious puberty there is apparently a premature activation of the gonadotropic functions. Just what initiates this activation is unknown. In hypogonadism the output of FSH by the pituitary is greatly increased just as it is following castration. Those dwarfs that mature sexually have a fusion of their epiphyses. Epiphyseal ossification to some extent parallels sexual development and other processes of maturation.

Friedgood (1946) said that the physiological age of an individual, as indicated by the state of epiphyseal-diaphyseal union, determines to a large extent the type of growth disturbance which can develop. The abnormal persistence of unossified epiphyseal cartilages in castrate or

eunuchoid individuals has been universally attributed to the absence or marked impairment of gonadal function. This assumption is supported by the fact that precocious puberty is associated with premature closure of the epiphyses and dwarfism, whereas normal sexual maturity likewise is related chronologically to epiphyseal union and cessation of growth. In both cases growth ceases. This, coupled with the fact that in castrated or eunuchoid individuals the epiphyses remain open indefinitely, has led to the widely accepted belief that the sex hormones inhibit growth. On the other hand, there is other evidence which indicates that the sex hormones stimulate growth. That androgen stimulates the rate of linear growth has been proved by the use of testosterone compounds in dwarfed children. Testicular development and acceleration of linear growth coincidentally have resulted from injections of chorionic gonadotropins. In neither case has there been evidence that these hormones induced premature closure of the epiphyses. It is also well recognized that the onset of puberty, which is characterized by increased androgenic and estrogenic activity, is associated with an increased rate of linear growth.

The sexual development of dwarf calves appears to be somewhat retarded, fertility is extremely low, and dwarf X dwarf matings fail to produce viable offspring. There is great difficulty in parturition, and most cases require Caesarean operation for delivery. Johnson et al (1950) and Lindley (1951) reported that histological studies of dwarf cattle gonads showed very little spermatogenesis in the tubules, with few sperm and hypoplasia of the germinal epithelium and interstitial cells.

Since it has been established that gonadal function is regulated by hypophyseal gonadotropins (Finerty, 1952; Heller, 1938) and since the sex hormones have been shown to influence growth, experiments were conducted to

determine whether or not there was a gonadotropic hormone deficiency in dwarf calves.

Procedure

Assays have been conducted using both the day-old cockerel and the hypophysectomized immature female rat. The chick assay used was that described by Evans et al (1940). Briefly, it consisted of subcutaneous injections of pituitary suspension in physiological saline twice daily for 5 days, sacrificing the birds 18 to 24 hours after the last injection and weighing the testes.

The assay procedure using hypophysectomized rats was essentially that of Evans et al (1940) and Heller et al (1938). Immature female rats hypophysectomized at 26 to 28 days were used. Intraperitoneal injections were started 14 days postoperative and continued daily for either 6 or 14 days. The time interval varied because the potency of these pituitary suspensions was being checked for other hormones on these same rats. The rats were sacrificed 18 to 24 hours following the last injection. The ovaries and uteri were dissected out and trimmed with the aid of a dissecting scope, blotted lightly and weighed on a precision balance. The capsule was removed from the ovaries, and the fluid was removed from the uteri prior to weighing.

Data and Results

A preliminary test of gonadotropic potency of the pituitary glands from dwarf calves was made in connection with an assay for thyrotropic potency using chicks. Apparently the level of injection sufficient to demonstrate the thyrotropic effect was too low to demonstrate the gonadotropic potency since the weight of the testes of the injected chicks was

not significantly heavier than the controls. It is of interest, however, to note that the chicks injected with a purified thyrotropic hormone preparation had significantly heavier testes than either the pituitary injected or control chicks.

Another chick assay designed specifically to test the gonadotropic potency of dwarf and normal calf glands showed no difference between them. The testes of these chicks were significantly heavier than the saline injected controls by more than 65 per cent, indicating that the level of injection was sufficiently high. A small group of chicks was injected daily with .06 cc of a purified preparation of gonadotropins as a positive control, and the increased testes weight in this group was nearly 300 per cent. These data are summarized in Table V A and B below. The mean weigh

TABLE V - GONADOTROPIC HORMONE ASSAY USING DAY-OLD CHICKS

Treatment	Total Inj. per chick	No. of Glands	No. of Chicks	Final Wt.(gm)	Wt. of Testes mgs	mgs%
Dwarf Calf Pit.	2.0 mgs.	1	9	45.8	17.1	37.8
	4.0 mgs.	1	8	49.0	13.1	26.8
Normal Calf Pit.	2.0 mgs.	1	11	58.1	22.2	38.3
	4.0 mgs.	1	8	58.8	23.0	39.1
Saline Control	0.4 ml.	0	20	55.5	19.1	34.4
Thyrotropin	0.8 mg.	0	10	57.0	23.8	42.4
Dwarf Calf Pit.	13.0 mgs.	5	28	61.0	22.3	36.3
Normal Calf Pit.	13.0 mgs.	5	27	61.0	22.9	37.5
Saline Controls	1.3 mls.	0	9	76.8	17.2	22.1
Gonadotropins	0.2 cc.	0	5	75.2	49.5	65.4

and standard errors of the testes were 22.1±1.5, 36.3±3.3, 37.5±2.1, and 65.4±7.6 for the saline control group, dwarf pituitary injected

group, normal pituitary injected group, and gonadotropin injected group, respectively .

A preliminary test for gonadotropic potency was conducted also in connection with a growth hormone assay using hypophysectomized immature female rats. A total of 61 mgs of acetone dried pituitary powder suspended in physiological saline was injected intraperitoneally over a 14-day period. The rats were sacrificed 18 to 24 hours after the last injection, and the ovaries were dissected free. Extraneous material was removed, and the ovaries were weighed on a precision balance. Using the weight of the capsulated ovaries as a measure of response, there was no significant difference between the dwarf and normal pituitary injected groups. However, the difference between the treated groups and the controls was highly significant. These data are shown in Table VI A. The mean weights and standard errors on a milligrams per cent of body weight basis were 9.7±1.8, 21.8±1.8, 25.6±1.8, and 51.0±1.6 for the saline injected control group, dwarf pituitary injected group, normal pituitary injected group, and the intact rats, respectively.

A later assay designed specifically to test the gonadotropic potency of the pituitaries of dwarf calves was conducted using hypophysectomized immature female rats. The measures of response were the increase in the weights of the ovaries and the uteri. The mean weights and standard errors of the uteri on a milligram per cent of body weight basis were 16.7± 2.6, 28.5±1.6, 35.1± 1.6, and 87.0±3.5 mgs per cent for the saline controls, normal pituitary, dwarf pituitary, and gonadotropin injected rats, respectively. All of these differences are highly significant. The mean weights and standard errors of the ovaries were 8.3 ±.9, 12.4 ±.6, 13.4 ± .6, and 25.1±3.2, respectively. The difference between the dwarf and

Hamburger (1950) reported that the uterine weight response was more constant than ovarian weight and that immature hypophysectomized rats were preferable as test animals for assays of unknown preparations.

Heller et al (1938) found that the uterus was much more sensitive to gonadotropic substances than the ovaries, requiring only about one-eighth as much material to obtain a significant increase in uterine weight as that required for a significant increase in ovarian weight. They found that the mean uterine weight could be used to determine the gonadotropic potency accurately with as few as 3 test animals.

These findings are similar to Smith and MacDowell's (1931) findings in dwarf mice. The testes of these dwarf mice were firm, and, although small, had the characteristic shape and appearance of normal testes. The seminal vesicles and other accessory glands were well developed. Sperm were present in many tubules but were not so numerous as in the testes of normal animals. The motility of sperm from both groups was equal. Consequently, they differed from hypophysectomized animals whose testes became flabby, sperm failed to develop, and whose accessory glands were greatly reduced in size. The reproductive system of the female did not reach so advanced a stage of development as the male.

The contrast of the reproductive system of these dwarf mice with that of hypophysectomized animals suggested to these workers that the defect might involve the suppression of the gonad-stimulating hormone. Consequently, they set up tests to determine if this were the case. They found that a unit of the anterior pituitary of the dwarf contained a greater concentration of the gonad-stimulating hormone than a unit of the anterior pituitary of the normal mature mouse. Therefore, the difference between the reproductive system in the dwarfs and the normals could be

interpreted as being due to a failure of the liberation of the hormone into the circulation by the dwarf.

Carroll et al (1951) reported finding the gonadotropic potency of the dwarf calf's pituitary as great as that of the normal calf but they did not report any excess in the dwarf gland.

When all of the evidence is considered, one is led to believe that the mechanism responsible for producing the dwarfed condition in these calves is also influencing the formation and/or release of gonadotropic hormones. Perhaps this is what one might expect from a review of the literature on dwarfism and hypogonadism in humans. The abnormal physiological action involved is not yet understood, however, and additional research is needed to shed light on this matter.

ADENOCORTICOTROPIC HORMONE ASSAYS

The adenocorticotropic hormone secreted by the adenohypophysis is known to regulate the production and release of the cortical hormones by the adrenal cortex (Long, 1942; Li and Evans, 1947; Sprague, 1951; Young, 1944). These adrenal cortical hormones are concerned with the metabolism of carbohydrates, proteins,and fats; with mineral and water balance; with intestinal absorption; and with protection of the animal against stresses (Long, 1942; Kendell, 1948; Sprague, 1951; Young, 1944).

The level of cortical hormones in the blood stream in turn regulates the release of ACTH from the pituitary (Turner, 1953; Sprague, 1951). Consequently, there is a reciprocal relationship between these two glands.

Many investigators have observed metabolic disturbances in dwarf cattle (Baker et al, 1951; Gregory et al, 1951, 1953; Chambers et al, 1954; Lindley, 1951). If these dwarfs live and have plenty of milk,they usually gain weight and fatten quite rapidly for the first two or three months,after which they often develop a "pot-belly" and begin to lose flesh. They not only lose the body fat, but the thick musculature found in many of these calves begins to dwindle away. Generally the older they get,the poorer their condition becomes. They are inclined to be chronic bloaters after they begin to eat roughages and grain,and many of them die as a result of bloating.

It has been reported that human dwarfs are characterized by low levels of blood sugar, increased sugar tolerance, abnormal sensitivity to insulin, and a moderately decreased or normal basal metabolic rate with a lower oxygen consumption. The adrenals are reported to be very

small and show hypoplastic changes in the cortical layers. In many cases autopsy revealed atrophy of the adenohypophysis (Friedgood, 1946).

Smith and MacDowell (1931) found a deficiency of ACTH in dwarf mice, and the adrenals were smaller than in normal mice. In this case, as with dwarf calves, the dwarf condition becomes more apparent as the animals reach weaning age and they begin eating solid foods.

With these facts in mind it was thought advisable to conduct assays to determine whether an ACTH deficiency existed in the pituitaries of dwarf calves.

Procedure

The assay procedures used in checking the ACTH potency of the pituitaries of dwarf and normal calves were essentially those of Bates et al (1940) with baby chicks and Simpson et al (1943) with hypophysectomized immature famale rats.

In brief, day-old White Leghorn-Black Australorp crossbred cockerels were injected subcutaneously twice daily for 6 days and sacrificed 18 to 24 hours following the last injection. The adrenals were removed and trimmed with the aid of a binocular loupe and weighed immediately on precision balances.

Immature female rats of the Sprague-Dawley strain were hypophysectomized at 26 to 28 days of age and the adrenals allowed to regress for a period of 14 days prior to starting the injections. The rats were allotted to individual cages at random for the entire experiment. In each case the whole pituitary gland was acetone dried, powdered, and suspended in neutral physiological saline for injection. Intraperitoneal injections were administered daily for 5 days,and the animals were autopsied 18 to 24 hours following the last injection. The adrenals were removed, trimmed

with the aid of a binocular loupe, and weighed on precision balances.

White (1945) showed that if the adrenal weights are expressed on the basis of 100 gms of body weight, assays in different laboratories can be more satisfactorily compared.

Data and Results

A check of the adrenal weights of 50 hypophysectomized immature female rats used in a growth hormone assay, in which a total of 61 mgs of pituitary powder was administered intraperitoneally daily over a 14-day period, showed no difference between the two groups injected with material from dwarf and normal calf glands. The weights of the adrenals were 15.8 mgs per cent for the dwarfs and 15.4 mgs per cent for the normals as compared to 12.4 mgs per cent for the saline injected controls. These data are shown in Table VII A.

Another assay using rats similar to those above was conducted in which each rat received intraperitoneal injections of 6 mgs of pituitary powder daily for 5 days. The mean adrenal weights of these rats on a mgs per cent of body weight basis were 15.1, 16.5 and 11.4 for the dwarf calf glands, normal calf glands, and saline injected controls, respectively. The difference between the controls and the pituitary injected groups is significant beyond the .01 level. The difference between the groups injected with dwarf and normal calf pituitary powder was not significant. These data are shown in Table VII B.

A third assay for ACTH was conducted using day-old chicks. Each chick received a total of 13 mgs of pituitary powder over a period of 6 days. Injections were administered subcutaneously twice daily. These data are summarized in Table VIII. On a milligrams per cent of body weight

TABLE VII - ADENOCORTICOTROPIC HORMONE ASSAY USING HYPOPHYSECTOMIZED IMMATURE FEMALE RATS

	Treatment	No. of Glands	No. of Rats	Total Mat. Inj./Rat	Final Wt. (gms)	Wt. of Adrenals mgs	mgs%
A				(14 days injection)			
	Dwarf Pit.	14	24	61.0 mgs	83.3	13.1	15.8±1.3
	Normal Pit.	8	10	61.0 mgs	75.3	11.4	15.4±1.2
	Hypo. Contr. [1]	0	7	saline	96.7	10.5	12.4±1.3
	Normal Contr.	0	9	saline	142.6	31.9	22.5±1.1
B				(5 days injection)			
	Dwarf Pit.	6	15	30.0 mgs	72.1	10.9	15.1±1.1
	Normal Pit.	6	17	30.0 mgs	73.2	12.0	16.5±1.0
	Hypo. Contr. [2]	0	15	saline	71.9	8.2	11.4±1.1
	Growth Horm.	0	10	2.5 mgs.	82.8	9.3	11.2±1.2
	Normal Contr.	0	10	saline	138.4	28.1	20.3±1.8

[1] Includes 5 rats which received growth hormone injection but which were no different from controls in adrenal weights in other assays.

[2] Includes 9 rats which received gonadotropic hormone but which were no different from controls either in weight or adrenal weight.

basis the mean weights and standard errors of the adrenals were 20.9±1.2, 20.6±1.2, and 15.9±1.2 for the groups injected with the dwarf calf glands, normal calf glands, and saline solution respectively. The difference between the controls and the pituitary-injected groups was highly significant. There was no difference between the groups receiving injections of pituitary suspension from dwarf and normal calves.

TABLE VIII - ACTH ASSAY USING DAY-OLD CHICKS

Treatment	No. of Glands	No. of Chicks	Total Mat. Inj./Chick	Final Wt.(gms)	Wt. of Adrenals Mgs	Mgs%
Dwarf Calf Pit.	5	28	13.0 mgs	61.5	12.6	20.9 ±1.2
Normal Calf Pit.	5	27	13.0 mgs	61.0	12.5	20.6 ±1.2
Saline Controls	0	9	saline	76.8	12.1	15.9 ±1.2

Discussion

Each of the three assays for ACTH discussed above indicated that there was no difference in the pituitary potency of ACTH between the dwarf and normal calf glands. Approximately 25 glands from dwarf calves and 20 glands from normal calves were used in these assays. There was considerable variation in response between the glands within each group. This variation appeared to be greater within the dwarf glands, the means ranging from 9.7 to 21.2 mgs per cent. However, statistical analysis of these differences failed to show significance.

PARATHYROID HORMONE STUDIES

Parathyroid hormone exerts a profound influence upon the metabolism of calcium and phosphorus and is responsible for the maintenance of these elements in the blood stream. Most of the calcium present in the body is stored in the skeletal system in the form of a calcium phosphate-carbonate compound. In the normal animal calcium is being deposited and absorbed from the bones continuously. Relatively small amounts of calcium are present in the blood plasma, chiefly in the form of calcium ions and calcium protienate. The level of calcium and phosphorus in the blood depends upon the dietary intake, factors which regulate the absorption and excretion of these elements, and the action of parathyroid hormone (Turner, 1953; Best and Taylor, 1950).

Robinson *et al* (1927) studied the effects of administering parathyroid extracts to normal dairy cattle. They found that serum calcium could be raised to 18 mgs per cent within 30 hours. At the same time there was a decrease in inorganic phosphorus with a marked increase in calcium and phosphate excretion in the urine. Visible manifestations were drowsiness and bloating. They observed that cattle were apparently less sensitive to parathyroid administration than dogs. Most of the experimental work has been done with laboratory animals.

The most predominant effect of a parathyroid deficiency is an increase in the ratio of phosphorus to calcium in the serum, whereas an excess of the hormone increases the calcium and reduces the phosphate ion concentration. Nearly all assay methods are based on these responses. The calcium and inorganic phosphorus levels are determined by direct blood analysis (Thorp, 1950).

Parathyroid deficiency in the rat leads to decalcification of the bones and disorganization of the enamel of the teeth. Chemical analyses show a relatively high magnesium content of the blood, which is, however, low in ash, calcium, and phosphorus. Cataractous lenses have been associated with parathyroid deficiencies in rats, dogs, and humans.

The mode of action of the parathyroid hormone is believed to be through its regulation of the osteoclasts and osteoblasts in the bone tissue and through its effect upon the excretion of phosphate by the kidney (Albright, 1941; Selye, 1932, 1942). One of the first responses to parathyroid extract is an increase in the number of osteoclasts, which correlates with the hypercalcemia and hypercalciuria. It is believed that the hormone initiates these cellular reactions in the bone and that the reabsorption of bone salts and of the organic matrix occurs as a consequence of these reactions. Heller et al (1950) showed that a single toxic dose of extract resulted in rapid reabsorption of bone followed by a somewhat slower regeneration. They traced the cellular transformation from one type to another which depended upon the presence or absence of the hormone.

Since this hormone is vitally concerned in skeletal development and integrity and since the main deficiency in dwarf calves appears to be in skeletal development, it was thought advisable to examine the possibility of abnormal parathyroid function. In addition to other abnormalities, many of these dwarf calves exhibit rachitic symptoms. In most rachitic animals the serum calcium and phosphorus are usually deficient (Best and Taylor, 1950).

Procedure

Blood samples were taken from a group of 15 known "carrier" cows and their dwarf calves when the calves were from one to three months of age. Samples were also taken from a similar group of cows believed to be free of the dwarf gene and their normal calves of comparable ages, breeds, and sexes. These blood samples were analyzed for calcium, phosphorus, and magnesium.

A second group of blood samples was taken from large and small type Hereford cows and their calves and analyzed for calcium, phosphorus, and magnesium.

A third group of blood samples was taken from 10 dwarf calves and 10 normal calves comparable in ages, breeds, and sexes and analyzed for phosphatase activity.

Data and Results

The mean values obtained for calcium, phosphorus, and magnesium for the various groups are shown in Table IX. These values are expressed in milligrams per 100 cc of serum.

These values fall within the normal range for beef cattle (Long, R. A., et al, 1952; Dukes, 1947), and there are no significant differences within the different age groups.

Analysis for phosphatase activity of the blood of 10 dwarf and 9 normal calves gave mean values of 20.73 and 19.82, respectively. These values are expressed in Bodansky units per milliliter of plasma.

TABLE IX - BLOOD ANALYSIS FOR CALCIUM, PHOSPHORUS, MAGNESIUM, AND PHOSPHATASE ACTIVITY

	Group	No. of Anim.	Milligrams Per Cent Ca.	P.	Mg.	Phosphatase
A	Carrier Her. Cows	15	9.19	6.41	1.87	6.2
	Clean Her. Cows	5	9.66	5.74	1.66	2.9
	Dwarf Her. Calves	13	10.30	8.57	1.54	2.7
	Normal Her. Calves	5	10.70	9.37	1.80	2.9
B	Large Type Her. Cows	4	9.95	3.82	2.27	
	Small Type Her. Cows[1]	5	10.10	5.00	2.40	
	Angus Cows	3	9.20	3.55	2.73	
	Large Type Calves	2	10.80	7.06	1.81	
	Small Type Calves	2	10.50	8.01	1.88	
	Angus Calves	2	10.70	6.13	2.45	

[1] These were known carrier cows

Discussion

According to some authorities calcification of bone is primarily dependent upon enzyme action. This enzyme is called phosphatase and is believed to be a product of the osteoblasts. Phosphatase is present in bone in largest amounts when and where active calcification is taking place, greater in ossifying cartilage and lesser in formed bone. Bone is apparently the main or only source of plasma phosphatase. It has been shown that plasma phosphatase is increased, often markedly, in diseases involving extensive changes in bone structure. Vitamin D is required, also, for in cases of Vitamin D deficiency an insufficient deposition of calcium and phosphorus is laid down, and the bones are soft

and easily deformed. Phosphatase activity in the blood is increased during rickets.

Osteoclastic activity is stimulated by the parathyroid hormone, and resorption of the bone is induced. On the other hand, osteoblasts show active proliferation when bone formation is in the ascendancy and alkaline phosphatase activity is high.

It can be seen from the discussion above that some measure of parathyroid activity, as well as the physiological condition of the bone, can be obtained by chemical analyses of the blood to determine the amount of calcium and inorganic phosphorus present, along with the alkaline phosphatase activity.

These analyses failed to show any significant differences between dwarf and normal cattle in the amount of calcium, phosphorus, and magnesium present in the plasma or in the alkaline phosphatase activity of these groups.

GENERAL DISCUSSION

It has been the purpose of this study to determine (1) whether there were endocrine abnormalities associated with dwarfism in beef cattle, (2) whether the same mechanisms were responsible in each of the different breeds, and (3) whether such abnormalities, if found, could be used to identify the "carrier" animals.

Pituitary glands were collected from approximately 75 dwarf calves and a somewhat smaller number from normal calves of the Hereford and Angus breeds and assayed for thyrotropic, gonadotropic, adrenocorticotropic, and growth hormone content using recommended assay procedures. Thyroid activity was also determined by blood analyses for protein-bound iodine content of the calves and by the weights of the thyroid glands. Parathyroid activity was determined by blood analyses for calcium and phosphorus levels and for phosphatase activity. Blood glucose levels were also determined for the dwarf and normal animals in support of the growth hormone assays.

The weights of the pituitaries of the dwarf and normal calves were compared. The data indicated that there was no significant difference in pituitary weights of dwarf and normal calves when differences due to age, weight, sex, and breed were considered. These data also failed to show any difference in pituitary weights of Hereford and Angus cattle.

A series of four assays, using the increased weight of the thyroids of the day-old cockerel as the measure of response, failed to show any significant difference in thyrotropic potency of dwarf and normal calf pituitary glands on a per unit basis. A total of 25 dwarf and 23 normal calf glands were assayed using a total of 410 chicks in this series.

Analysis of blood serum from groups of normal and dwarf calves showed no significant differences in protein-bound iodine content. A comparison of a limited number of glands failed to reveal any significant difference in weight when expressed on a percentage of body weight basis and when consideration was given to differences in breed, sex, and age. However, the thyroids of the Angus calves were considerably heavier than those of the Hereford calves.

Three assays were conducted to measure the growth hormone potency of normal and dwarf calf pituitaries, using both plateaued and hypophysectomized female rats as the assay animals. The measures of response in the plateaued female rats were (1) increase in body weight and (2) increase in tail length. The measures of response in the hypophysectomized immature female rats included (1) increase in body weight, (2) increase in tail length, (3) increase in width of the epiphyseal cartilage plate of the tibia, (4) blood sugar, (5) blood sedimentation rate, and (6) serum phosphatase activity. A total of 26 dwarf and 17 normal calf glands and 72 rats were used in the plateaued rat assay over a 21-day injection period. In the two hypophysectomized rats assays, 126 rats were used, 86 of them injected with the pituitary powder from 21 dwarf and 16 normal calf glands. The data from these assays strongly indicate that there was a greater amount of growth hormone stored in the dwarf pituitary gland than in the same amount of pituitary from a normal calf. Since the dwarf calves fail to grow at a normal rate, the indication is that, even though the hormone may be produced, it is perhaps not being released in sufficient amounts for normal growth. Blood analyses, however, from groups of dwarf and normal calves failed to show significant differences in level of blood glucose or phosphatase activity between them. Although the

difference in blood glucose was not significant, it was in favor of the dwarf calves. The means and standard errors were 51.84± 4.47 and 39.47± 5.48 for the dwarfs and normals, respectively.

A similar condition was found in the gonadotropic hormone content of dwarf calf pituitaries. When the increased weight of the ovaries was used as the measure of response of gonadotropic activity, no significant differences were observed. However, when the increased weight of the uterus was used as the measure of response, there was a highly significant difference in favor of the gonadotropic hormone content of dwarf calf pituitaries. The mean uterine weights were 16.7, 35.1, 28.5, 90.9, and 81.0 mgs per cent of body weight for the hypophysectomized controls, dwarf pituitary, normal pituitary, saline-injected intact rats, and gonadotropic hormone injected rats, respectively. The data indicate that dwarf calf pituitaries contained a greater amount of gonadotropic hormones on a per unit basis than did normal calf pituitaries.

Assays were conducted to compare the ACTH potency of the pituitaries from dwarf and normal calves using approximately 25 glands from dwarf calves and 20 glands from normal calves. The mean adrenal weights of day-old chicks injected twice daily for 5 days were 15.9, 20.9 and 20.6 mgs per cent of body weight for the saline controls, dwarf pituitary and normal pituitary injected groups, respectively. The mean difference between the pituitary injected groups and the controls is significant beyond the .01 level. The mean adrenal weights of hypophysectomized immature female rats injected daily for 5 days were 11.4, 15.1 and 16.5 mgs per cent of body weight for the saline controls, dwarf pituitary and normal pituitary-injected rats, respectively. The difference between the dwarf and the normal pituitary-injected groups is not statistically

significant; however, the difference between the control group and the pituitary injected groups was highly significant.

The parathyroid hormone activity of dwarf and normal calves and of different cow groups was compared indirectly from analyses of blood data. A group of "carrier" cows and their dwarf calves were compared with a similar group of "clean" cows and their normal calves. Large-type Hereford cows and their calves were also compared with known "carrier" cows of comprest breeding and their calves. The calcium, phosphorus, and magnesium values for all groups fell within the normal range of values for beef cattle. There were no significant differences between the "carrier" and "clean" cows or between the normal and dwarf calves. It must be concluded, therefore, that the parathyroid hormone appears to be functioning normally in the dwarf calf and in known "carrier" cows.

Heredity is known to exert an important effect on the growth of an individual. Many authorities have associated this hereditary influence with the functioning of the endocrine system of the individual. It has been shown that the regulation of body growth and size is largely dependent upon the proper functioning of the anterior pituitary,which induces its effect primarily by direct action on the tissues of the organism. It also influences growth indirectly through its control of the thyroids, gonads, adrenals, and perhaps the pancreas. The secretions of these glands are essential to the optimal growth-promoting function of the anterior pituitary.

It appears that the primary factor limiting growth in dwarf calves is the failure of normal skeletal development,which is probably due to a malfunction of the anterior pituitary. This malfunction of the pituitary probably is the result of the genetic constitution of the tissues

in the presence of the dwarf gene. Apparently one pair of genes in the homozygous condition is able to swing the physiological processes of the animal out of balance and causes the dwarfed condition. However, there must be many other genes which modify the expression of dwarfism. Such an arrangement as this is known to be involved in the inheritance of several characters in domestic animals. Bates (1942) points out that whether or not such a trait as dwarfism in mice is developed may be determined by a single gene but that such a gene cannot produce the trait without the cooperation of many other genes.

If one assumes that the dwarf gene mediates its effects by way of the pituitary gland,he must also assume that the normal pituitary is functioning during embryological development. According to Moore (1950) most of the experimental evidence in mammals suggests that there is some influence by the pituitary during this period.

It is well known that castration of an animal results in an increase in the proportion of basophils in the anterior pituitary. Experimental thyroidectomy results in a marked decrease in the acidophils,which are believed to elaborate the growth hormone. Apparently the reduction in the proportion of acidophils following thyroidectomy is more pronounced than that which occurs following castration. Friedgood (1946) says that the functional pattern of the pituitary appears to be such that hypersecretion of one of its hormones is frequently associated with an increase in the rate of secretion of another of its hormones.

The data from this study indicate that there was an increased amount of growth and gonadotropic hormones in the pituitaries of dwarf calves. If true, this may indicate that the release mechanism for growth hormone at least was not functioning properly and that an insufficient quantity

was being released to stimulate normal growth. These data indicate that the production of ACTH, thyrotropin, thyroxin, and parathyroid hormones in the dwarf calf was not different from that of the normal calf. Moore points out that the presence of an active substance in the gland does not assure that it exerts an influence upon development. This has been clearly demonstrated in amphibian larvae, in dwarf mice, and in immature rats. It would be most helpful to know the amount of growth and gonadotropic hormones circulating in the blood stream of dwarf calves. This would indicate whether the hormones are being released by the gland or whether the tissues are incapable of responding to the hormonal substances.

It was mentioned earlier that many factors are capable of influencing the formation, release, and metabolism of hormones. The nutritive state of the organism is of particular importance. Since there appears to be metabolic disturbances associated with dwarfism in cattle and the condition of the animal becomes poorer with age, this may be an important factor in the release and metabolism of these hormones. Ershoff (1952) pointed out that the gonadotropic hormones are likely to be increased during inanition and early starvation.

Shelton (1942) classified dwarfism in humans under five main headings. The classification which includes hypopituitarism and hypothyroidism is that of nutritional disturbances. He claims that these types of dwarfism result from an inadequate utilization or deposition of the essential elements for growth and development. He says the active principles of the endocrine glands are the utilizers of foods, chemicals, and vitamins and cannot be separated from this important function.

Additional research is needed to confirm or disprove the findings of excessive growth and gonadotropic hormones in the present assays, as

well as to determine the metabolic conditions of dwarf calves. Histological studies of bone biopsies from dwarf and normal calves at various stages of growth should also shed some light on the processes of abnormal bone formation in the dwarfs. Histological sections of all of the major endocrine organs from both normal and dwarf calves of the same age, sex, and line of breeding are now being prepared.

At present it appears that the same mechanisms are responsible for dwarfism in both the Hereford and Angus breeds. No satisfactory method has yet been found to distinguish between those animals that are carrying the dwarf gene in a heterozygous condition and those that are free of it.

SUMMARY AND CONCLUSIONS

A study was conducted in an effort to determine (1) whether there are endocrine abnormalities associated with dwarfism in beef cattle, (2) whether the same mechanisms are responsible within the different breeds, and (3) whether the experimental results could be used to identify the "carrier" animals.

Assays were conducted to compare the potency of thyrotropic, growth, gonadotropic, and adenocorticotropic hormones in dwarf and normal calf pituitaries. Thyroid activity of the two groups was also checked by blood analysis for serum protein-bound iodine and by comparison of the weights of the thyroid glands. Parathyroid activity was compared by blood analyses for calcium and phosphorus levels and for phosphatase activity. Blood glucose levels were also compared. The pituitary weights were compared on both the trimmed, fresh whole glands and on the dried glandular powder obtained from these glands.

The data indicated that:

1. There was no significant difference in thyrotropic or adenocorticotropic hormone content of the pituitaries of dwarf and normal calves.

2. There was no significant difference between thyroid or parathyroid activity of dwarf and normal calves.

3. The growth and gonadotropic hormones of dwarf calf pituitaries were more potent than those found in equal amounts of pituitary powder from normal calves.

4. When consideration was given to differences in breed, sex, age, and/or weight of calf, the differences in pituitary and thyroid weights of dwarf and normal calves were small.

5. The thyroids from Angus calves were considerably heavier than those from Hereford calves, but there was no difference between their pituitary weights.

6. The blood levels of calcium, phosphorus, magnesium, serum protein-bound iodine, glucose, and phosphatase activity in the dwarf calf were not different from those of the normal calf.

7. The same mechanisms seemed to be responsible for dwarfism in the Hereford and Angus breeds.

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APPENDIX

TABLE X - SUMMARY OF CHICK ASSAY NO. 1 FOR THYROTROPIC HORMONE
(Summer, 1952)

Gland		Sex	1 mg (.05cc) Level of Injection No. of Chicks	Chick Av. Wt.	Thyroid Av. Wt.	2 mgs(.10cc) No. of Chicks	Level of Injection Chick Av. Wt.	Thyroid Av. Wt.
Trial 1								
Dwarfs	Angus	M	5	57	5.9	-	-	-
	Angus	M	5	60	6.0	5	51	5.6
	Angus	F	5	59	6.1	5	63	5.7
	Angus	F	5	58	5.0	5	59	6.3
	Hereford	F	3	61	4.4	-	-	-
			23	59	5.5	15	58	5.9
Normals	Hereford	F	5	61	7.0	-	-	-
	Angus	F	5	60	5.9	4	58	6.6
	Shorthorn	F	5	57	5.6	-	-	-
	H X A	F	5	58	6.2	4	50	4.8
			20	59	6.2	8	54	5.7
Saline Controls			11	64	4.1	10	60	3.6
Trial 2				.33 mg level			.67 mg level	
Angus Dwarf		F	9	87	6.2	8	86	5.8
Angus Normal		F	11	94	7.5	10	100	7.4
Saline Control			7	92	4.7	-	-	-

TABLE XI - SUMMARY OF CHICK ASSAY NO. 2 FOR THYROTROPIC HORMONE
(Spring, 1953)

Glands	Sex	Approx. Age (mos.)	Calf Wt. (lbs.)	No. of Chicks	Av. Chick Weight	Thyroid Wts. per Level of Injection .1 mg	.5 mg	1.0 mg	Ave.
Dwarf Calves									
Hereford	F	1	60	15	72.5	4.16	4.28	6.16	4.87
Hereford	M	1	52	15	72.3	5.28	7.90	6.00	6.42
Angus	M	4	164	15	72.3	3.80	4.76	5.44	4.67
Angus	F	1	104	15	75.7	5.48	7.18	5.24	5.97
Hereford	F	3	315	15	69.8	3.66	4.88	5.44	4.66
Hereford	M	2	99	15	71.9	4.28	5.38	7.18	5.61
Total		12		90	434.5	26.66	34.38	35.46	32.20
Average		2			72.4	4.44	5.73	5.91	5.37
Normal Calves									
Hereford 24	M	11	790	15	72.1	4.12	6.04	7.20	5.73
Hereford 23	M	11	800	14	71.9	7.28	6.20	6.75	6.74
Angus 132	M	12	890	15	78.8	5.64	5.44	9.62	6.90
Hereford 21	F	8	570	15	78.1	5.06	6.26	6.20	5.63
Total		42		59	300.9	22.10	23.94	29.77	25.27
Average		10.5			75.2	5.53	5.99	7.44	6.32
Saline-Injected Controls						.05 ml	.10 ml		
				12	76.6	4.37			
				11	71.2		4.42		
Total or Average				23	73.9	4.37	4.42		4.39

TABLE XII - SUMMARY OF CHICK ASSAY NO. 3 FOR THYROTROPIC HORMONE
(Fall, 1953)

Calf	Sex	Approx. Age	Wt. lbs.	No. of Chicks	Chick Wt.	Thyroid Wt. per Level of Inj. .5 mg level mgs	mgs%	1.0 mg level mgs	mgs%
Dwarfs									
Her. 310	F	1 mo.	70	16	62.9	5.80	9.09	6.23	10.09
Her. 1288	F	2 mo.	73	20	47.3	4.89	10.97	5.73	11.68
Total or Av.		1.5	72	36	54.2	5.30	10.13	5.95	10.97
Normals									
Her. 1650	F	7 mo.	459	20	62.8	6.13	10.27	7.56	12.05
Her. 785	F	9 mo.	608	17	46.7	4.89	9.37	5.73	10.49
Total or Av.		8.0	534	37	60.8	5.56	10.23	6.72	11.25
Saline Controls		-	-	19	57.7	5.15	8.78	5.15	8.78
Thyrotropin		-	-	10	57.0	-	-	10.30	18.18

TABLE XIII - SUMMARY OF CHICK ASSAY NO. 4B FOR THYROTROPIC HORMONE
(March, 1954)

Treatment	Sex	Approx. Age	Weight lbs.	No. of Chicks	Chick Wt.	Thyroid Wt. Mgs	Mgs%
Dwarfs							
Ang. H-73	F	3 mo.	195	6	60.1	5.1	8.2
Ang. H-83	F	3 mo.	105	6	63.7	4.5	7.3
Her. J-3	F	5 mo.	300	6	57.9	5.6	10.4
Her. W-2	F	6 mo.	300	5	60.9	4.4	7.4
Her. W-5	M	5 mo.	150	5	61.6	5.9	9.7
Total or Av.	5	4.4 mo.	210	28	60.9	5.1	8.6
Normals							
Ang. 359	M	4 mo.	400	6	59.9	7.5	12.5
Ang. 1567	S	5 mo.	395	4	64.0	4.3	5.4
Her. 7270	F	5 mo.	398	6	57.9	7.2	12.4
Her. 7200	F	5 mo.	391	5	62.0	5.8	9.4
Her. 7289	M	4 mo.	336	6	62.4	3.8	6.1
Total or Av.	5	4.6 mo.	385	27	61.0	5.8	9.4
Saline Controls		-	-	9	76.8	5.3	6.9
Thyrotropic Hormone			-	10	64.3	10.8	18.8

TABLE XIV - SUMMARY OF HYPOPHYSECTOMIZED RAT ASSAY NO. 1
(14-day injection period--Jan., 1954)

Treatment	No. of Rats	Fin. Wt. (gms)	Gain or Loss Bd. Wt. (gms)	Tail L. (mm)	Width of Epiphyseal Plate (micra)	Wt. of Glands in Mg% of Body Weight Thyroids	Ovaries	Adrenals	Blood Sugar	Sed. Rate
Dwarf Calf Pit										
Angus	7	84.1	16.9	3.71	132.3	6.63	19.78	14.87	89.4	1.1
Her.(Conv.)	9	79.2	16.0	5.33	162.3	6.70	22.51	16.35	78.7	2.8
Her.(Comprest)	8	88.6	21.4	7.38	152.7	6.34	22.76	16.10	101.6	2.1
Weighted Average	24	83.8	18.0	5.58	148.6	6.55	21.80	15.83	88.9	1.86
Normal Calf Pit										
Angus	6	75.3	10.7	3.67	127.2	6.27	24.68	15.43	82.0	1.3
Hereford	5	74.2	8.6	3.60	139.0	6.32	26.86	15.28	81.8	1.5
Weighted Average	11	74.8	9.7	3.64	133.1	6.30	25.55	15.37	82.0	1.38
Control (Hypo)	3	55.0	-5.3	0.00	74.9	5.33	11.67	13.67	92.0	0.75
Growth Horm.	5	102.4	35.4	16.20	211.1	5.18	6.20	10.98	108.1	6.10
Normal Rats	10	141.9	51.6	23.10	195.6	6.97	50.99	22.48	117.9	1.60

TABLE XV - SUMMARY OF HYPOPHYSECTOMIZED RAT ASSAY NO. 2
(March, 1954)

Treatment	No. of Rats	Final Weight	Gain in Weight	Wt. of Glands in mgs% of Body Weight Uteri	Ovaries	Thyroids	Adrenals
Hereford Dwarfs							
W-1F	3	70.0	1.7	36.7	12.4	5.3	14.6
W-3F	3	72.3	6.3	28.8	8.2	4.4	14.0
C-1F	1	67.0	-1.0	31.3	-	7.5	16.7
J-4F	2	78.5	8.5	23.5	17.7	5.4	15.4
J-1M	3	69.3	1.0	32.8	13.1	6.8	9.7
9747M	3	74.3	7.7	43.1	12.8	6.6	21.2
Weighted Average	15	72.1	4.4	35.1	13.4	5.8	15.1
Hereford Normals							
802F	3	74.7	7.3	25.8	11.0	5.1	18.9
880F	3	70.0	4.3	29.3	12.8	5.1	14.6
860F	3	80.0	8.7	26.5	11.0	5.3	15.6
7223F	3	71.0	3.3	31.4	15.2	7.4	20.0
696M	2	79.0	5.0	27.3	8.4	6.9	12.8
500M	3	66.7	1.8	30.4	16.1	7.0	15.8
Weighted Average	17	73.2	4.9	28.5	12.4	6.1	16.5
Controls(Hypo.Rats)	6	72.8	3.5	16.7	8.3	5.7	11.8
Gonadotropic Hormone	9	71.3	2.1	87.0	25.1	4.7	11.1
Growth Hormone	10	82.8	12.9	21.3	11.8	5.9	11.2
Normal Rats	10	138.4	27.3	90.9	26.9	4.8	20.3

TABLE XVI - BLOOD ANALYSES FROM DWARF AND NORMAL BEEF CATTLE

Type of Animals	No.	Calcium	Magnesium	Phosphorus	Phosphatase Units/ml plasma
Normal Cows	94	10.4	1.2	5.47	2.1
	627	10.0	1.9	4.92	1.7
	678	9.1	1.5	7.13	1.8
	158	8.3	1.8	5.80	6.3
	501	10.5	1.9	5.38	2.6
Average		9.66	1.66	5.74	2.9
Normal Calves					
	316	9.1	1.9	8.74	2.8
	158	11.7	1.5	9.11	3.5
	317	11.0	1.7	11.18	3.2
	627	10.3	2.0	8.92	1.7
	501	11.5	1.9	8.92	2.9
Average		10.7	1.8	9.37	2.8
"Carrier" Cows					
	01	9.8	1.7	6.72	12.0
	02	9.1	1.7	6.58	6.7
	03	7.8	1.9	6.44	1.6
	04	9.4	1.7	5.57	1.9
	05	9.0	1.8	5.98	4.6
	06	11.1	2.3	5.80	23.8
	08	9.2	1.7	5.01	3.1
	10	9.3	1.5	6.35	2.9
	12	8.9	2.0	7.36	2.3
	14	9.9	2.0	7.22	17.1
	15	6.1	2.0	6.72	4.3
	16	9.4	2.0	6.90	0.9
	18	10.1	1.8	7.27	5.7
	22	9.4	2.0	6.72	5.0
	23	9.4	2.0	5.52	1.2
Average		9.19	1.87	6.41	6.2
Dwarf Calves					
	1283	10.3	1.2	7.91	3.5
	1285	10.8	1.7	9.52	1.9
	1288	11.2	1.8	8.79	1.7
	1290	10.2	1.7	8.51	3.2
	1292	11.9	1.5	9.29	3.5
	39	8.0	1.4	8.05	3.2
	1284	10.7	1.9	9.29	3.3
	1286	11.0	1.9	10.40	3.7
	1287	9.5	1.7	7.13	2.5
	1289	9.5	1.2	7.91	1.0
	1291	9.9	1.2	8.05	2.5
	1293	9.6	1.5	7.82	2.8
	1294	11.6	1.3	8.74	2.5
Average		10.3	1.54	8.57	2.7

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