SOME CARBOHYDRATE METABOLISM STUDIES WITH DWARF AND NON-DWARF BEEF CATTLE

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INTRODUCTION

Many different forms of dwarfism have been reported in animals, including man. Usually the occurrence of these dwarfs was quite sporadic and was regarded as a curiosity rather than posing a problem to the species.

During the early part of this decade a dwarf type which has been called "snorter," "short-headed," or "brachycephalic" was reported in Hereford cattle. During the next few years the occurrence of snorter dwarfism in the Hereford and Angus breeds increased rapidly and people associated with the beef cattle industry became concerned.

A considerable amount of research was then directed toward a study of dwarfism, with the early work attempting to find the cause of dwarfism. Most of the geneticists agreed that snorter dwarfism was inherited as a simple, single autosomal recessive gene. With this information it was known that genetic carriers were in existence, which were phenotypically indistinguishable from animals free of dwarfism. Consequently, most of the subsequent research has been directed toward the development of a technique which would differentiate between carrier and clean cattle.

A few diagnostic tests have been proposed, however, none have been accurate enough to be accepted by the beef cattle industry. To compensate for the lack of an accurate diagnostic technique, breeders have resorted to the use of progeny testing and primarily pedigree selection in an effort to control dwarfism. Pedigree selection, although effective

against dwarfism, is costly to the breed because it reduces the selection potential that exists within the population. Many outstanding animals are discriminated against because dwarfism has been associated with some of their ancestors. Progress in the improvement of the important economic characteristics of beef cattle are retarded because these characteristics are emphasized less in the selection program. The progeny test for dwarfism has been used primarily by the purebred breeders. A very important limitation of the progeny test, besides the cost involved, is the time interval required before the necessary information can be obtained. For all practical purposes the test is limited to bulls because of the small number of offspring a cow can produce.

Pedigree selection and progeny testing have been effective as indicated by the decline in the number of dwarf calves in recent years. These methods, however, will not eliminate dwarfism. Many carrier animals remain undetected and keep the dwarf gene in existence in the population. Should the breeders relax their efforts in maintaining these control measures, dwarfism could easily again pose a serious problem to the beef cattle industry.

The primary purpose of this study was to subject snorter dwarf and normal appearing cattle to various tests in an attempt to measure differences in carbohydrate metabolism. By studying some of the more fundamental aspects of the physiology of dwarfism, it was hoped the results might provide a basis for developing an accurate diagnostic test.

REVIEW OF LITERATURE

Dwarfism in Beef Cattle

A number of kinds of dwarfs and dwarf-like conditions have been reported in nearly all breeds of beef and dairy cattle. The "bulldog" calf of the Dexter-Kerry cattle was described as early as 1904. These monsters were usually aborted after six to eight months of pregnancy. They had short rounded heads, extremely short limbs, bulging crania, depressed noses and protruding lower jaws. This lethal was caused by a dominant gene in the homozygous state. Crew (1923) concluded that the bulldog condition was due to a hypofunctioning of the pituitary. The bulldog condition has been reported in other breeds of cattle. Carmichael (1933) reported its occurrence in Nganda cattle, Brandt (1941) in Guernsey cattle, and Berger and Innes (1948) in Friesian herds. Johannson (1953) described a new kind of achondroplasia in Swedish cattle. Endocrine disturbances were evident. One normal bull, mated to unrelated cows of various descent, produced 28 normal and 25 malformed calves. It was assumed that the defective animals were heterozygous for a gene for achondroplasia, and that this gene had arisen by mutation in the pre-germinal tissue of the sire of the malformed calves. Arrillaga (1949) described dwarfs among Puerto Rican cattle which had reduced body length and shorter cannon bones. Cole and Moore (1942) reported a hydrocephalic condition in Holstein-Friesian cattle and suggested a simple recessive gene as the cause. Mead et al. (1942) reported a new type of proportionate dwarfism

in a herd of Jersey cattle. These dwarfs were not distinguishable at birth, but they grew more slowly and were distinguishable at one year of age. The inheritance of this type of dwarfism appeared to be due to a simple autosomal recessive factor.

Craft and Orr (1924) described a dwarf Hereford calf. The symptoms exhibited by the calf were similar to those observed in cases of cretinism in man. An examination of the thyroid, parathyroid, and pituitary glands revealed that they were markedly underdeveloped. Lush (1930) described the "duck-legged" Hereford cattle in Texas. The noticeable characteristic of these cattle was the shortening of the long bones of the limbs. Baker et al. (1950) reported an achondroplasia in Shorthorn cattle. There appeared to be a metabolic disturbance as most of the animals were usually thin. The cause of this condition was believed to be due to a simple autosomal recessive gene. Baker et al. (1951) reported the occurrence of dwarfism in Aberdeen-Angus cattle. The dwarfs were exceptionally compact and lowset. At a later age their heads appeared longer and narrower than at two to three months of age. They concluded that this type of dwarfism was governed by a single autosomal recessive gene.

Yager et al. (1955) described nine different types of dwarfs occurring in the British and Brahman breeds of beef cattle. The snorter dwarf, occurring primarily in the Hereford and Angus breeds, was reported to be the most frequent type.

Johnson et al. (1950) first described a type of dwarfism in Hereford cattle which did not resemble too closely other dwarf types previously mentioned in the literature. Although their data were available on only one herd, they had reports showing that the defect was occurring in many

purebred herds and that the incidence of dwarfs appeared to be increasing. Early observations on "midget" cattle in Washington were reported by Lindley (1951).

Description of the Snorter Dwarf:

No one dwarf is likely to express all of the characteristics which have been associated with dwarfism. Neither is any one of these characteristics likely to be expressed in all dwarfs. It should also be pointed out that not only do the dwarfs vary in the kind of abnormalities, but also in the degree of expression of these abnormalities.

Johnson et al. (1950), Lindley (1951), Gregory et al. (1951), and Pahnish et al. (1955a) have given a phenotypic description of the snorter dwarf. The following description will be the more obvious characteristics of snorter dwarfism which the above workers have reported. In general, the more apparent symptoms are progressive and become increasingly pronounced with age. Body size is reduced. The long bones are reduced in length and increased in thickness, sometimes with marked distortion of the limbs and/or flexed pasterns. One of the traits most often noted is the abnormality of the head. Most dwarfs have bulging foreheads, short wide muzzles, protruding lower jaws, and prominent eyes. There is usually a "bulldog" condition of the face presenting a dished-in appearance. There may also be an enlargement and protrusion of the tongue. Dyspnea of both an inspiratory and expiratory nature is observed. Most dwarfs are very susceptible to all types of respiratory disturbances. Post-natal mortality is high, and only a few live to maturity. By three or four months the paunch becomes distended; after that the tendency to chronic bloat is marked. Muscular incoordination associated with spastic tremors

is common, especially following excitement. An impaired sexual activity of the dwarfs has also been noted.

Inheritance of Dwarfism:

Johnson et al. (1950) suggested that the defect was inherited as a monofactorial, autosomal recessive. The same mode of inheritance was reported by Lush and Hazel (1952) after analyzing breeding records collected by the American Hereford Association. Pahnish et al. (1955b) conducted critical mating tests and confirmed that snorter dwarfism was inherited as a simple autosomal recessive.

Gregory and Carrol (1956) reported that the same dwarf gene is common to both the Hereford and Aberdeen-Angus breeds.

Chambers et al. (1954) obtained some snorter dwarf calves from comprest cows mated to non-comprest bulls that were carriers of the snorter dwarf gene. Their data indicated that the genes responsible for dwarfism in comprest and conventional Hereford and Angus cattle may be allelic, or that the comprest cattle in the test also carried a high frequency of the recessive dwarf gene found in non-comprest cattle.

Gregory (1955 and 1956) studied the genetic relationships between different types of dwarfs in the three major beef breeds. He suggested that all of the dwarf phenotypes tested were a part of the same genetic complex and that modifying genes were involved which differentiated specific dwarf phenotypes. Dollahon (1958) mated a number of different types of dwarfs and reported that the different dwarfs were related genetically, but the exact relationship was not determined.

Warwick (1958) suggested two possibilities as to why snorter dwarfism increased to such a high frequency. First, it is possible that breeders

could have selected for the dwarf gene accidently if, purely as a matter of chance, the dwarf gene had occurred in a few particularly popular sires. The bulk of evidence indicates that this probably did not account for the increase in dwarfism, although the possibility cannot be entirely ruled out. The second possibility is that the gene is not completely recessive and that the heterozygous, or carrier animals, exhibit certain characteristics which cause breeders to favor them in selection; thus increasing the frequency of the dwarf gene. Arthaud et al. (1957) reported that heterozygous calves had shorter, wider cannon bones than calves with clean pedigrees. This could be one factor favoring the selection of the heterozygote if such favoritism exists.

Anatomical Studies:

The skeletal modifications are the most obvious differences between dwarf and normal appearing cattle. Gregory et al. (1951) reported that the head contours of dwarf and normal cattle were markedly different, and that the outstanding characteristic of snorter dwarfism was a brachycephalic head with a mid-forehead prominence. This prominence was present at birth and persisted throughout life. Gregory and Brown (1952) developed the profilometer for studying head form in the bovine. Gregory et al. (1952) and Gregory et al. (1953) measured the head profiles of horned Hereford bulls with the use of the profilometer and suggested the use of this method in the field to detect dwarf carrier animals. A number of workers have questioned the accuracy of this method and its use in the field has been very limited.

Emmerson and Hazel (1956) and Hazel et al. (1956) reported that dwarf calves exhibited severe longitudinal compression and irregular protrusion

of the ventral surface of the bodies of the lumbar vertebrae. Most heterozygotes exhibited similar abnormalities of a less extreme nature. This abnormality was suggested as a possible means of identifying carrier animals; however, some vertebrae classifications did not agree with the dwarfism genotype of the calves. Buchanan et al. (1956) reported similar vertebrae abnormalities in dwarf calves. They also noted the large amount of variation that existed in the skeletal abnormalities within the snorter type of dwarf. Turman et al. (1957) found that x-ray classification and genotype were not always in agreement. High et al. (1958) concluded that the x-ray method for the identification of individual animals with respect to genotype for dwarfism was not highly accurate, but that it was highly accurate in identifying snorter dwarf calves.

Bovard et al. (1956) and Buchanan et al. (1956) observed that the total length of the lumbar vertebrae was shorter in the dwarfs. Tyler et al. (1957) reported that the most disproportionate bones in the dwarf were the metacarpal bones and that reduced diaphyseal lengths were responsible. Evidence was presented indicating the reduction in the length of the diaphyses occurred in utero.

The premature closure of the spheno-occipital synchondrosis was detected in bovine dwarfs of the short-headed variety and reported by Julian et al. (1956) and Julian et al. (1957). Buchanan et al. (1956) reported that the dwarf exhibited pinched occipital condyles of the skull.

Most of the anatomical studies have been concerned with skeletal modifications, however, Eveleth et al. (1956) observed that the dwarf heart is abnormal, being almost spheroid in shape.

Physiological Studies:

Carrol et al. (1951) reported that the pituitaries from dwarf beef cattle were deficient in thyrotropic hormone, and that this would account considerably for the failure of the dwarf calves to grow. Marlowe and Chambers (1954) and Fransen and Andrews (1954) failed to find significant differences in the thyrotropic hormone potency of dwarf and normal calf pituitaries. Using I^{131} Crenshaw and Turner (1954) and Crenshaw et al. (1957) reported normal uptake by the thyroid of the dwarf, and could not demonstrate a subnormal secretion of pituitary thyrotropin in dwarf beef cattle. Cornelius et al. (1956) reported that serum protein-bound iodine and cholesterol in dwarf calves was within the normal range reported for beef cattle. Fransen and Andrews (1958) reported that the blood plasma of dwarfs contained significantly less cholesterol than non-dwarf animals.

Marlowe and Chambers (1954) reported that pituitaries from dwarf calves contained more growth hormone and gonadotropic hormone than pituitaries from non-dwarf calves. Fransen and Andrews (1954) found no difference in the pituitary gonadotropic activity between dwarf and non-dwarf calves.

Andrews and Fransen (1958) administered thyroactive iodinated protein, testosterone propionate and diethylstilbesterol, either singly or in combination, to dwarfs, but failed to produce evidence that the dwarfism syndrome could be corrected by therapy with these hormones.

Fransen and Andrews (1954) reported the occurrence of a number of cystic pituitaries and/or cystic adrenals in dwarfs. Lindley (1951) also reported cystic pituitaries in dwarf cattle.

Fransen (1955) observed that hematological, electrocardiogram, pulse, respiration, and body temperature values of dwarfs were within the normal range reported for beef cattle. Cerebrospinal fluid pressure was abnormally high in the dwarf animals and the brain, pituitary, and thyroid reportedly grew at a faster rate.

Hafez et al. (1958) reported that dwarfs had significantly lower respiration rates, whereas rectal temperatures and pulse rates were almost identical to those of non-dwarf animals. Among hematological values studied, the dwarfs showed lower blood hemoglobin, hematocrit, and white cell count. The electrophoretic analysis of plasma proteins did not show characteristic patterns. Ruminal protozoa, in dwarfs classified as bloaters, were either absent or in reduced numbers and showed sluggish motility.

Cornelius et al. (1956) reported average values for calcium, phosphorus, magnesium, total protein, plasma proteins, packed cell volume, hemoglobin, white blood cells, and red blood cells in 38 snorter dwarfs. All chemical and hematological values appeared to be in the normal range with the exception of differential white blood cell counts, in which the dwarfs were significantly lower in lymphocytes and significantly higher in neutrophils.

Deyoe et al. (1957) measured plasma free glutamic acid, glycine, and histidine after insulin induced stress in dwarf and normal animals. No significant differences in the responses were detected. Total leucocyte counts and differential white cell counts were also made following the injection of crystalline zinc insulin. Two hours after insulin significant increases were obtained in the dwarf carrier animals and dwarfs, but

not in animals from a herd in which there had been no incidence of dwarfism. Differential counts indicated the change was due to an increase in neutrophils and a slight decrease in eosinophils.

Foley et al. (1956) used the increase in the white cell count in the blood, following intravenous insulin, to test for an adrenal cortical hormone response to stress. Dwarfs responded very little, pedigree-clean animals showed a rapid and extreme response, whereas known carriers of the dwarf gene were intermediate in their response to this treatment. Differences between the three groups were highly significant when tested statistically. This test has been publicized quite widely as the insulin test for dwarfism. Massey et al. (1958) reported on the progress of the insulin test. The test had been conducted on about 1,800 animals of various breeds, ages, and sex in different parts of the country and under various climatic conditions. They stated that there was a differential response between pedigree-clean and carrier animals as measured by this test, however, from 10 to 15 percent did not give a clear-cut response. They listed several factors which were known to affect the accuracy of the test. First, and probably the most important, was the human error involved in making blood cell counts. Secondly, animals which underwent stress before the test was conducted affected the accuracy of the test. The temperament of the animals and quick changes in the weather were suspected of interfering with the response to insulin.

Massey et al. (1958) injected pedigree-clean, carrier and dwarf animals with two doses of insulin, 48 hours apart and measured red blood cell fragility in a 0.48 percent sodium chloride solution. The red blood cells of the pedigree-clean animals were more resistant than the carriers

and dwarfs, but there was considerable overlap between the three groups. The differences were greater when fragility was measured after the second insulin injection and there was less overlap between the three groups. Results similar to these were also obtained after the intravenous injection of ACTH. A significant difference was observed between pedigree-clean and carrier animals in the resistance of the red blood cells to a hypotonic NaCl solution within five hours after the injection of the hormone. Dwarfs responded in a manner similar to carriers in this respect, although on the average their red cells were less resistant.

Carbohydrate Metabolism Studies:

Marlowe (1954) determined blood glucose on 10 dwarfs and nine non-dwarfs. He found the values to be 51.8 milligrams percent and 39.5 milligrams percent respectively. Fransen (1955), using a similar number of animals, found an average of 50.5 milligrams percent for the dwarfs and 65.0 milligrams percent for the controls. The differences obtained in the above two experiments were not statistically significant.

Preliminary results reported by Buchanan (1957) showed that after a 72 hour fast, pedigree-clean cattle contained nearly twice as much liver glycogen as dwarf and dwarf carrier animals. These differences were highly significant. After eight days of high carbohydrate feeding, the dwarf and carrier animals were not consistent in their utilization of the carbohydrate. Approximately one-half of each group had a high liver glycogen content while the other half were still low in that respect. The pedigree-clean group was quite uniform, all having a high content of liver glycogen after the carbohydrate feeding.

Heidenreich et al. (1955) subjected nine calves, including dwarf and normal appearing individuals, to insulin-glucose tolerance tests. Very little difference was noted between the two groups and the tolerance curves of the dwarf calves were not of a consistent pattern. Tolerance tests were also conducted on 10 mature cows. No apparent difference in metabolic response was noted between dwarf carrier and non-carrier cows. Lactating cows, however, showed a decreased tolerance to glucose when compared with non-lactating cows.

Weaver et al. (1957) administered intravenous injections of glucose to 20 dwarf cows, bulls and calves. Thirty minutes after these injections the blood sugar level in the dwarfs was extremely high, but within one to two and one-half hours it had returned to normal. It was concluded from this that the dwarfs were not lacking in ability to lower their blood sugar to the pre-injection level after glucose injections.

Foley et al. (1956) utilized 59 animals from the Angus and Hereford breeds to determine the possible causes of dwarfism in beef cattle. Insulin tolerance tests, in which insulin was injected intravenously and the blood sugar determined at regular intervals for periods up to 12.5 hours following this treatment, showed definite differences between dwarf and normal appearing animals. The tests indicated that the blood sugar level dropped much more quickly and to a lower level in the dwarfs and failed to return to the pre-injection level as quickly as in normal appearing animals. They postulated a possible abnormal pituitary or adrenal hormone response to stress in the dwarfs.

Deyoe et al. (1957) determined blood glucose in association with insulin induced stress in dwarf and normal animals and detected no

significant differences in the responses obtained.

Massey et al. (1958) subjected dwarf, carrier, and pedigree-clean animals to two intravenous injections of insulin, 48 hours apart. Approximately 12 to 14 animals were included in each group. The first injection was 0.8 unit of insulin per kilogram of body weight and the second dose, 0.3 unit. It was hoped the two injections, a few hours apart, would minimize environmental influences. Blood samples were obtained through 12 hours following insulin administration. When the heavier dosage of insulin (0.8 unit) was given, average differences between pedigree-clean and both carrier and dwarf animals were considerable. At the lighter dosage (0.3 unit) no definite difference was noted in pedigree-clean and carrier animals, both being able to return their blood glucose to the initial level within the time limit studied. The dwarfs, however, were unable to do this. Because of the increased insulin sensitivity of the dwarf and carrier animals, these workers felt there may be a deficiency in one or more of the pituitary hormones, or that the hormones may be present but unable to function properly in the regulation of carbohydrate metabolism.

Massey et al. (1958) measured the response of pedigree-clean, carrier and dwarf cattle to intravenous injections of adrenaline. Four c.c. of a 1:10,000 solution of adrenaline was given to each animal regardless of size and age. Blood samples were taken through 10 hours following treatment with this hormone. The limited results indicated that there was a differential response of the three groups to this hormone, as measured by blood sugar changes. In the dwarf, the injection of the hormone caused a slight increase in the blood sugar level; in the carrier, it caused a

rapid increase in blood glucose in 30 minutes followed by a rapid drop at one hour, and in the pedigree-clean cows the rise was rapid and was much slower in returning to normal than in the carriers. These workers also reported that following intravenous injections of ACTH there was essentially no difference between the three groups of cattle, as far as changes in blood glucose and white blood cells were concerned.

Factors Influencing Blood Glucose in Ruminants

Dukes (1955) gives the range of blood glucose for mature ruminants to be from 30 to 70 milligrams percent with the range for cattle being 40 to 70 milligrams percent. Glucose is one of the most variable constituents in the blood of ruminants and the variation is even greater if young ruminants are included. Some of the reasons for the wide variation will be reviewed.

Age:

The blood glucose levels of newborn ruminants approximate those of nonruminant mammals, which are approximately 100 milligrams percent, however, the glucose in the blood decreases early in life until adult values are reached (Hodgson et al. 1932, Jarrett and Potter 1952, Kennedy et al. 1939, Kronfeld 1957, McCandless and Dye 1950, and Reid 1953). The above workers agreed that the decrease in blood glucose was most rapid during the first few weeks of life, but they were in variance as to when adult levels were reached. For sheep the extremes reported as to when adult levels were reached varied from six to 13 weeks while for cattle 10 weeks to two years was the range.

The reason for the change in the blood glucose level is not entirely agreed upon. McCandless and Dye (1950) noted that the changes in blood glucose in young lambs and calves closely paralleled the functional development of the rumen and they offered this as a possible explanation. Reid (1953) also determined the decline of blood glucose in young lambs and found that a large portion of the decline in whole-blood glucose was accounted for by a steady and almost complete disappearance of glucose from the corpuscles. Because adult levels of blood glucose were reached before adult levels of volatile fatty acids, Reid concluded that the decline in blood glucose was largely due to factors other than the functional development of the rumen. Kronfeld (1957) reported that adult levels of blood glucose were reached in lambs two to four weeks before rumination was observed and concluded that the decline was probably not entirely due to the development of rumen function. Vandersall et al. (1957) and King et al. (1956), working with calves and lambs respectively, confirmed Reid's work by reporting that the decline in blood glucose was due largely to the glucose loss of the corpuscles.

Nutrition:

Cameron and Goss (1940) reported that no significant differences in blood glucose were observed when ewes were subjected to different nutritive conditions. Although the nutritive regimes were not widely different, the ewes receiving the highest energy ration had the highest average blood glucose.

Sampson and Boley (1940) reported that various rations, fed for short periods of time, significantly affected the glucose content of the

blood of ewes. The higher energy ration resulted in the higher blood glucose values.

Reid (1950a) reported that blood glucose was not affected by the plane of nutrition. Turk and Work (1933) varied the fat content of rations of six lactating cows from seven to one percent and reported that there was no relationship between the fat or carbohydrate intake and blood sugar level.

Diurnal and Seasonal:

Hodgson et al. (1932), Zarrow et al. (1952), and Sampson and Boley (1940) reported that there was essentially no diurnal variation in the blood glucose of mature ruminants.

Reid (1950a) found that there was only a very small rise in the blood glucose of sheep after feeding. The afternoon samples gave higher glucose values than the morning samples, but the differences were small and very little diurnal variation existed.

Magee (1932) and Allcroft and Strand (1933) fed high carbohydrate rations to goats and sheep, respectively. They measured the blood glucose after feeding and found either no change or only slight increases in glucose content of the blood.

Kennedy et al. (1939) reported that there was a diurnal variation in the glucose content of calves' blood. Directly after feeding milk, blood sugar values increased sharply. The reason for the differences in diurnal variation between young and mature ruminants can be explained on the basis of rumen function.

Elsden (1945), Gray et al. (1952), and Phillipson and McAnally (1942) have clearly demonstrated that glucose and other dietary carbohydrates are

rapidly fermented to volatile fatty acids in the functional rumen. Thus, glucose undergoes this change and is not absorbed as such. In the young ruminant, before the rumen becomes functional, the feed goes directly to the abomasum. Glucose remains unchanged and is absorbed by the intestines as in simple stomached mammals.

Horrocks and Paterson (1957) reported a seasonal variation for glucose in the blood of dairy cattle. Blood glucose was significantly lower in the winter than in the other seasons tested. Braun (1946) reported a significant seasonal difference in the blood glucose of cattle.

Fasting:

Sampson and Boley (1940) reported that fasting ewes for seven and eight days resulted in decreases in blood glucose of 23 and 15 percent respectively.

Hodgson et al. (1932) fasted five heifers for nine days. The blood glucose had dropped only slightly after three days of fasting, but it had decreased approximately 50 percent at the end of the nine day fast. The glucose level of the blood did not return immediately to the pre-fast level upon feeding, but required several days.

Reid (1950a) reported that fasting for a period of 24 or 46 hours had little effect on the blood sugar level in non-pregnant sheep which were in good condition. The blood glucose was significantly different from the pre-fasting level after a four day fast. A fast of 24 hours duration produced a marked hypoglycemia in ewes in poor body condition. It was more pronounced during the last two months of gestation with blood glucose levels as low as eight milligrams percent being recorded. Allcroft and Strand (1933) reported that a seven day fast did not appreciably

alter the blood sugar of sheep.

Magee (1932) fasted two goats for a period of seven days. He reported that the glucose of the blood dropped approximately 40 percent until 40 hours, then a gradual increase resulted until the initial level was nearly reached at the end of the seven day fast.

Exercise, Excitement, and Epinephrine:

Exercise, excitement, and epinephrine elevate the glucose content of the blood. It is generally believed that exercise and excitement produce the blood glucose rise by increasing the release of epinephrine from the adrenal medulla.

Sampson and Boley (1940) subjected ewes to moderate exercise by walking them rapidly for 15 minutes. Only a slight increase in the blood sugar resulted. When the ewes were subjected to vigorous exercise, running for 10 minutes, large increases in the blood glucose were observed. Increases as high as 100 percent were not uncommon.

Allcroft and Strand (1933) reported that driving ewes quietly for 15 minutes did not greatly influence the blood sugar level, however, in some cases it was increased. Sheep that were kept running for periods of 15 to 30 minutes showed sizeable increases in blood glucose after the vigorous exercise. These workers also demonstrated increases in the glucose content of the blood of sheep subjected to a barking dog. Evidence was also produced which indicated that high blood glucose values might result due to excitement during sampling. Dougherty et al. (1956) reported that the excitement of handling, dosing, and bleeding caused an appreciable rise in the blood glucose of sheep. Hodgson (1932) reported that four

cows, subjected to the sight of a dog, responded by an average increase in blood sugar of 11 percent. When the dog was allowed to bark there was a further increase of 43 percent in the glucose content of the blood. All four of the cows showed a definite increase. Cutler (1934) reported an increase of 90 percent in the blood glucose of goats after five minutes of excitement.

The increase in blood glucose after excitement is believed to be due to the secretion of epinephrine by the adrenal medulla. Epinephrine injections into ruminants have been shown to increase the blood glucose (Cutler 1934, Massey et al. 1958, Zarrow et al. 1952). Strand et al. (1934) reported that the blood sugar in adrenalectomized sheep was definitely lowered. No changes occurred in the blood glucose of adrenalectomized sheep when they were subjected to the types of excitement and muscular exercise used by Allcroft and Strand (1933). This would support the theory that epinephrine was secreted during the excitement of the animal.

It is obvious that the handling and the temperament of the animals can greatly influence the blood glucose levels. This could easily account for many of the variable results reported, especially those where only a few numbers have been used.

Miscellaneous Factors:

Hodgson et al. (1932) reported that there were no significant differences in blood glucose between Ayrshire, Guernsey, Holstein, and Jersey breeds of dairy cattle. Cows giving a liberal flow of milk were found to have slightly less blood sugar than dry cows or those yielding a small

quantity of milk. There was always a definite rise in blood glucose in association with estrus, but observations were limited in this area.

Hewitt (1930) reported blood glucose values considerably lower for lactating cows in comparison to non-lactating cows. Heifers, during their estrus period, were noted to have extremely high blood glucose readings. Reihart (1939) determined the blood glucose on 60 lactating and 20 non-lactating cows and found no apparent difference between the two groups. Fish (1928) reported that lactation or pregnancy had little influence on the glucose content of the blood of cows.

Kronfeld (1957) found that during pregnancy in ewes the concentration of glucose remained within the pre-pregnant range. Reid (1950a) also reported that gestation had little effect on blood glucose, although the values were somewhat lower the last two months of gestation.

Insulin Tolerance

Zarrow et al. (1952) injected two sheep with 25 units of insulin. The insulin produced a hypoglycemia within a half hour and a maximum depression in blood glucose of 52 percent resulted. Thereafter, the blood sugar began to rise, returning to pre-injection levels in six hours.

Brown et al. (1936) and Petersen et al. (1931) reported the effects of injecting large intravenous doses of insulin into dairy cows. Doses up to 800 units were administered in 25 minutes with no convulsions or coma noted in any of the cows, even though in some cases the blood sugar was lowered to 10 milligrams percent. Fasting the animals for 48 hours before giving insulin did not produce convulsive signs. Hitchcock and Phillipson (1946) reported similar findings in sheep.

Jasper (1953), using limited numbers, reported that in dairy cows the intravenous injection of two units of insulin per kilogram of body weight gave a maximum effect in reducing blood glucose, whereas one unit did not. Increasing the insulin dosage to 10 units per kilogram increased the duration, but not the depth of hypoglycemia. The rate of fall of blood glucose after insulin was relatively constant and not related to insulin dosage. He also reported that prolonged insulin hypoglycemia, usually 30 to 36 hours, resulted in a convulsive, hypoglycemia crisis, which responded well to glucose injections.

Reid (1951a) reported that in ruminants the rate of fall of blood glucose following intravenous insulin was considerably slower than in non-ruminants. Dosage levels were as high as 10 units per kilogram of body weight with no observable, severe hypoglycemic signs. Reid (1951b) described the neurological signs associated with insulin hypoglycemia in sheep. Some convulsions were observed when extremely large doses of insulin were given. Convulsive activity was seen only after the blood glucose had been reduced to negligible levels, less than one milligram percent, and had remained there for upwards of one hour.

Jarrett and Potter (1953) reported that adult sheep fasted from one to four days, then given massive doses of insulin, failed to show convulsions. Successive intravenous insulin injections were given to maintain the blood glucose at 10 milligrams percent for 15 to 18 hours with no abnormal signs resulting from the prolonged hypoglycemia. However, when the splanchnic nerve was sectioned in the adult sheep, insulin caused convulsions. Intravenous insulin injections into young lambs resulted in convulsions, but as the lambs increased in age it required more insulin

and a longer period before the convulsive signs appeared. The subcutaneous injection of insulin into adult sheep resulted in convulsions.

Setchell and McClymont (1955) injected ewes with insulin both intravaneously and subcutaneously. Most of the ewes injected subcutaneously went into convulsions and died, while no convulsive signs were observed in the ewes injected intravenously. It appeared the blood glucose remained low for a longer period of time in the ewes which received the subcutaneous injections.

Reid (1950b) produced evidence which would indicate that ruminants depend less upon glucose for an energy source than non-ruminants. This might help explain why insulin shock is rarely encountered in ruminants.

Glucose Tolerance

Kennedy et al. (1939) reported that when mature cattle were drenched with glucose (0.75 grams per kilogram of body weight) there was little change in the blood glucose level, whereas in young calves a marked hyperglycemia was noted. Dollar and Porter (1957) reported an approximate increase in blood glucose of 100 percent after drenching young calves with a glucose solution.

Bell and Jones (1945) drenched ten adult bovines with as much as eight grams per kilogram of body weight and observed that the variations in blood glucose were within the range of normal fluctuation.

Hodgson et al. (1932) used a stomach pump to administer six to nine pounds of glucose to seven dairy cows. In all cases an increase in blood glucose resulted and in some instances 200 percent increases were observed. It is very likely that because of the tremendous amounts of glucose given

some passed into the abomasum escaping rumen fermentation. Reid (1952) obtained blood glucose curves after direct administration of glucose into the abomasum of adult sheep. He concluded that although glucose absorption occurred from the intestine the rate, when compared to non-ruminants, was low.

Dougherty et al. (1956) reported that the oral administration of 3.7 grams of glucose per kilogram of body weight caused distinct rises in jugular blood glucose levels in four ruminants. Orally administered glucose at 1.5 grams per kilogram of body weight in one steer caused an increase in blood glucose. However, the same dosage in two sheep caused no significant change. These workers also observed that excitement, dosing, and bleeding of the animals caused appreciable rises in blood glucose.

Holmes (1951) reported that after the intravenous injection of 0.3 gram of glucose per kilogram of body weight into dairy cows it required from three-fourths hour to two and one-half hours for the blood glucose to return to pre-injection levels.

Goetsch et al. (1956) conducted glucose tolerance tests on 12 yearling Hereford heifers. A 50 percent glucose solution was injected at the rate of 0.5 gram per kilogram of body weight. The time required for the injection was approximately five minutes. Two minutes after glucose infusion there was a seven fold increase and at thirty minutes a two fold increase in the glucose content of the blood over the pre-injection blood glucose level. Six hours after the glucose injection the blood glucose was nearly back to the initial level. Of the total amount of glucose injected, approximately 10 percent was excreted in the urine during the six hour period.

Jarrett and Potter (1952) and McCandless and Dye (1950) reported that the tolerance time in young ruminants, after intravenous glucose, was approximately 90 minutes (about the same as for non-ruminants) while three to five hours were required for the glucose to return to initial levels in adult ruminants. As the young ruminants became older, the duration of the hyperglycemia gradually increased until their tolerance for glucose was the same as adult ruminants.

Reid (1952) measured arterio-venous blood glucose differences at peak hyperglycemia and insulin hypoglycemia in adult sheep. He found that the A-V differences were relatively small as compared to those of non-ruminants. He also suggested that the low rate of extrahepatic glucose assimilation at hyperglycemic levels provided a partial explanation for the relatively slow rate of clearance of injected glucose from the general circulation of ruminants.

Holmes (1951) reported that pregnancy did not appreciably alter the tolerance for glucose in cows, however, a 48 hour fast did decrease the tolerance for glucose. Seven hours after glucose administration the blood glucose was still above the pre-injection level. McCandless et al. (1948) reported that after the intravenous injection of one gram of glucose per kilogram of body weight into non-fasted sheep the glucose returned to initial levels in about four to six hours after the glucose infusion. However, in sheep fasted for five to six days before receiving the same dosage of glucose, the blood glucose was still above pre-injection levels 11 hours after glucose administration.

Reid (1958) reported that in glucose tolerance tests with sheep the rate of glucose disappearance was slow in sheep fed on roughage diets,

but rates as high as those usually observed in man were recorded when the sheep were receiving high intakes of a diet containing 50 percent cracked maize. The blood glucose often returned to levels as much as 11 milligrams percent below the pre-injection level.

MATERIALS AND METHODS

The majority of the cattle utilized for the various tests were from three projects at the Fort Reno Experiment Station, El Reno, Oklahoma. Project 873, "Evaluation of Methods for Identifying Dwarf Carriers in Beef Cattle," contributed most of the animals. This project consists of a herd of approximately 100 known carrier cows of both the Angus and Hereford breeds and 10 "comprest" Hereford cows. In addition approximately 20 dwarfs of both sexes and breeds are maintained as part of the project.

Twelve yearling Hereford heifers and 16 Angus and Hereford calves were used from Project 670, "The Improvement of Beef Cattle by the Application of Breeding Methods." This project consists of three unrelated lines of breeding, one Angus and two Hereford lines. These animals are under excellent range conditions and receive good management.

Twelve cows were used from Project 650 at Fort Reno. This project, "The Relation of Nutrition and Age at First Calving to Lifetime Performance of Beef Cattle," consists of grade Hereford cows. These cows graze native grass pastures during the summer. In the winter they are placed in their respective groups of low, medium, and high levels of winter feeding.

In all cases the response measured, after subjecting the animals to various tests, was the glucose content of the blood. Blood was collected from the jugular vein into tubes containing approximately twenty milligrams of sodium fluoride per milliliter of blood. Sodium fluoride was

used as the anticoagulant because in addition to its anticoagulating property it inhibits the glycolytic decomposition of blood glucose (Roe et al. 1927). During the early part of this study the blood had to be transported from Fort Reno to Stillwater before the analysis could be done. Thus, the sodium fluoride provided a precautionary measure against the deterioration of the glucose in the blood.

The blood samples were analyzed in duplicate in the Biochemistry Department at Oklahoma State University, using the Nelson-Somogyi method (Nelson 1944 and Somogyi 1945). This method employs the use of a barium hydroxide-zinc sulfate procedure to deproteinize the blood which gives a filtrate containing practically no reducing substances other than glucose. The barium-zinc filtrate is heated with an alkaline copper reagent and treated with a special arsenomolybdate color reagent. The color developed is compared with that obtained from a known amount of glucose. The optical density of blood samples prepared in such a manner were read in a Coleman Model 6A Junior Spectrophotometer at a wavelength of 540 mu. The amount of glucose in each sample was calculated from the following formula:

$$\frac{\text{optical density of unknown}}{\text{optical density of standard}} \times \text{mg. glucose in standard} \times \frac{100}{0.025} = \text{mg. glucose per 100 ml. blood}$$

Duplicate samples with differences in optical density which showed an error greater than ten percent were re-analyzed.

These data were analyzed statistically by methods described by Snedecor (1956).

A more detailed procedure for each experimental phase will precede the results of that particular phase.

RESULTS AND DISCUSSION

Epinephrine Studies with Sheep

Preliminary studies were conducted on seven yearling western wethers in an effort to establish safe dosage levels and response to epinephrine. It was anticipated that the information could be applied to cattle since both are ruminants and their blood glucose values are comparable.

The sheep all weighed approximately 100 pounds, and were maintained on a ration of ground milo plus prairie and alfalfa hay. Each of three trials consisted of three treatments with two wethers per treatment. A 1:1000 solution of Epinephrine Hydrochloride Injection, No. 3350-39, from Lederle Laboratories was used. The epinephrine was diluted with sterile saline to 1:10,000 just prior to the time of injection. All injections were made intravenously into the jugular vein. The epinephrine was injected through the same needle from which the initial blood sample had been collected. The blood samples were analyzed for glucose as soon as possible following the final bleedings.

The results of three trials representing a total of nine treatments are presented in tables I and II. The treatments in Trial A were as follows: treatment I consisted of injecting a total dose of 0.25 c.c. epinephrine per 100 pounds of body weight into each of two wethers; in treatment II each wether received 0.25 c.c. epinephrine per 100 pounds of body weight which was divided into three equal parts and injected at five

TABLE I EFFECT OF DIFFERENT LEVELS OF EPINEPHRINE ON THE BLOOD GLUCOSE OF WESTERN WETHERS
(mg. per 100 ml. blood)

Trial	Treatment	No.	Minutes After Initial Epinephrine Injection								
			0	5	10	20	30	40	60	80	120
A	I	2	60.6	93.0	96.9	104.1	103.0				
	II	2	69.6	85.3	92.0	103.6	101.6				
	III	2	70.6		91.8	104.0	112.6				
B	IV	2	43.7			76.9		82.8	81.0		
	V	2	46.0			73.0		98.6	100.0		
	VI	2	51.2			73.0		93.0	111.2		
C	VII	2	57.7			101.8		122.3	151.0	167.8	196.4
	VIII	2	64.4			104.4		134.0	157.0	148.6	
	IX	2	54.4		83.4	105.2	117.6	122.1	150.4		

TABLE II CHANGES IN THE BLOOD GLUCOSE OF WESTERN WETHERS INJECTED WITH DIFFERENT LEVELS OF EPINEPHRINE

Trial	Treatment	No.	Percent Increase from the Initial Glucose Value to the Various Sampling Times (in minutes)							
			0-5	0-10	0-20	0-30	0-40	0-60	0-80	0-120
A	I	2	52.5	59.6[b]	71.4[b]	69.9				
	II	2	22.3[a]	32.6	48.4	45.6				
	III	2		30.3	47.6	59.9				
B	IV	2			76.6		90.0[c]	85.8		
	V	2			57.2		114.5	117.3		
	VI	2			43.6		81.3	116.0		
C	VII	2			76.4		111.9	161.6	190.6	240.4
	VIII	2			62.4		108.2	145.0	130.9	
	IX	2		52.8	93.2	115.4	123.2	176.6		

[a]Different from treatment I ($P < .10$).

[b]($P < .005$) between the treatments in that particular trial.

[c]($P < .10$) between the treatments in that particular trial.

minute intervals; and in treatment III each wether received 0.25 c.c. epinephrine per 100 pounds of body weight divided into three equal parts and injected at 10 minute intervals. In all treatment groups blood samples were taken at 0, 10, 20, and 30 minutes, with a sample taken at five minutes in treatments I and II.

The actual glucose values for the three treatments are quite similar at all the sampling times with no significant differences existing between the three groups. Ten minutes after the initial epinephrine injection the glucose values, in milligrams percent, were 96.9 for treatment I, 92.0 for treatment II, and 91.8 for treatment III. For the thirty minute sampling period the glucose values were 103.0, 101.6, and 112.6 milligrams percent for treatments I, II, and III respectively. When the glucose values were expressed as a percent increase from the initial level, the responsesof the three treatments were different. At all sampling times, treatment I resulted in larger increases in blood glucose than the other two treatments. The larger increases in blood glucose in treatment I might have resulted because the initial blood glucose level of the wethers in treatment I was 60.6 milligrams percent, nearly 10 milligrams percent lower than the blood glucose of the wethers in the other two treatments.

Highly significant ($P < .005$) differences in the blood glucose increases existed between treatments at 10 and 20 minutes following epinephrine. The largest mean differences were at 10 minutes following epinephrine where the increases were 59.6% for treatment I, 32.6% for treatment II, and 30.3% for treatment III. These data show that larger increases in blood glucose resulted from a total dose of 0.25 c.c. epinephrine at one injection rather than splitting the dose and injecting the parts at five or 10 minute intervals.

The treatments in Trial B were as follows: treatment IV consisted of injecting a total dose of 0.50 c.c. epinephrine into each wether; in treatment V each wether received a total dose of 0.50 c.c. epinephrine divided into two equal parts and injected at 20 minute intervals; and in treatment VI each wether received a total dose of 0.75 c.c. epinephrine divided into three equal parts and injected at 20 minute intervals. Blood samples were obtained at 20 minute intervals over a 60 minute period.

No significant differences were found for actual glucose values between the treatments of Trial B (table I). The initial glucose values for treatments IV, V, and VI were 43.7, 46.0, and 51.2 milligrams percent. Sixty minutes after the initial epinephrine injection the blood glucose values were 81.0 milligrams percent for treatment IV, 100.0 milligrams percent for treatment V, and 111.2 milligrams percent for treatment VI. Twenty minutes after epinephrine, treatment IV had produced the greatest increase in blood glucose over initial levels, but the smallest increase 60 minutes after the initial epinephrine injection (table II). The increases 60 minutes after epinephrine were 85.8%, 117.3%, and 116.0% for treatments IV, V, and VI respectively.

In Trial C each wether received a total dose of 1.5 c.c. epinephrine. In treatment VII the dose was divided into six equal parts and injected at 20 minute intervals. In treatment VIII the dose was divided into three equal parts and injected at 20 minute intervals, while in treatment IX the dose was divided into six equal parts and injected at 10 minute intervals. No significant differences between treatments resulted from either an analysis of the actual glucose values (table I) or the percent increases (table II). Treatment VIII resulted in the smallest blood glucose increases

throughout the time intervals studied. Sixty minutes after the initial epinephrine injection the percent increases in blood glucose were 161.6, 145.0, and 176.6 for treatments VII, VIII, and IX respectively. Results from this trial demonstrated that tremendous increases in blood glucose could be produced by the periodic injection of epinephrine every 10 or 20 minutes. Two hours after the initial epinephrine injection treatment VII produced an average increase of 240.4 percent in the glucose content of the blood.

Epinephrine produces the characteristic hyperglycemia by causing a shift in the equilibrium reaction between inactive and active phosphorylase (Sutherland and Cori 1951). This liver enzyme is believed to catalyze the rate limiting step in liver glycogenolysis, so that when more active phosphorylase is present an immediate rise in blood glucose results. Epinephrine also causes the breakdown of muscle glycogen into lactic acid which can be transformed into glucose in the liver (Cori and Cori 1928b). This effect of epinephrine appears to be much slower than the effect on the phosphorylase system.

The results of trial B differed from those of trial A. In trial B, splitting the total dose and injecting it at various time intervals resulted in larger increases in blood glucose. The opposite was true in trial A. It is very probable that at any one time there is a known quantity of phosphorylase enzyme in the liver. If all of the enzyme is active as a result of a certain dosage of epinephrine, then any additional epinephrine would not cause an additional rise in the blood glucose. Epinephrine is oxidized very rapidly after administered intravenously. Its potential in producing a hyperglycemia is limited if it does not produce

its effect in a few minutes. As the epinephrine is destroyed more of the active phosphorylase shifts back to the inactive form. This could possibly explain the difference obtained between trial A and B. These data suggested that there was a maximum effective dose at any one injection time and if the maximum dose was exceeded, little or no additional response resulted. Twenty minutes after epinephrine the percent increases over the initial glucose values were 71.4 for treatment I and 76.6 for treatment IV. The response was nearly the same for both treatments, although the dosage level for treatment IV was twice that for treatment I. This would suggest that the epinephrine injection in treatment IV was above the maximum dose. Until the maximum dose is reached it is most likely that the maximum response would result from a single injection rather than splitting the dose. The same trend was indicated in Trial C. The results of this trial showed that it was not only the size of the dose but also that the time interval between injections was important in determining the maximum glucose response. The treatments in Trial C gave similar responses at nearly all sampling times where they were comparable. However, large differences between treatments existed when the end results were considered. Based on the percent increase 10 or 20 minutes following the final epinephrine injection, the values were 240.4%, 145.0%, and 176.6% for treatments VII, VIII, and IX respectively.

In the final experimental phase with sheep three wethers were fasted for sixty-three hours and three wethers received the ration previously mentioned. Each wether received a total dose of 1.5 c.c. epinephrine per 100 pounds body weight divided into six equal parts and injected at twenty

minute intervals. Periodic samples were taken during two and one-half hours following the first epinephrine injection. The effect of epinephrine injections in fasted and fed wethers is shown in tables III and IV.

Table III shows the effect of epinephrine on the actual blood glucose values. Sixty-three hours of fasting resulted in a significantly ($P < .005$) lower initial blood glucose in the fasted wethers than in wethers which remained on feed during this time. The initial value for the fasted group was 48.7 milligrams percent as compared to 66.0 milligrams percent for the fed group. After the intravenous injection of epinephrine the differences in the blood glucose of the fasted and fed groups were significant at all sampling times. The differences between the two groups were decreasing in magnitude as the sampling time after the initial injection of epinephrine increased. Two and one-half hours after the initial epinephrine injection the blood glucose values were 140.2 milligrams percent for the fasted wethers and 195.9 milligrams percent for the fed wethers. The difference between the two groups at this sampling time was significant ($P < .05$).

Table IV expresses the blood glucose values as a percent increase from the initial glucose value. The fed wethers had a greater percent increase in blood glucose throughout the 150 minute period. The largest difference ($P < .025$) which existed between the two groups was forty minutes following the initial epinephrine injection. The percent increases over initial levels at this sampling time were 59.6 and 98.6 for the fasted and fed groups respectively. The difference between the two groups diminished considerably as the sampling time increased. One-hundred-fifty minutes after the initial injection of epinephrine the percent increases

TABLE III BLOOD GLUCOSE VALUES OF FASTED AND FED WESTERN WETHERS INJECTED WITH EPINEPHRINE
(mg. per 100 ml. blood)

Group	No.	Minutes After Initial Epinephrine Injection				
		0	40	80	120	150
Fasted	3	48.7[b]	77.8[b]	103.2[c]	134.8[c]	140.2[d]
		(7.56)[a]	(13.97)	(22.78)	(24.98)	(25.33)
Fed	3	66.0	131.0	164.9	201.7	195.9
		(2.31)	(7.91)	(7.16)	(7.51)	(15.72)

[a]Standard deviation.

[b]Different from the fed group ($P < .005$).

[c]Different from the fed group ($P < .025$).

[d]Different from the fed group ($P < .05$).

TABLE IV CHANGES IN THE BLOOD GLUCOSE OF FASTED AND FED WESTERN WETHERS INJECTED WITH EPINEPHRINE

Group	No.	Percent Increase from the Initial Glucose Value to the Various Sampling Times (in minutes)			
		0-40	0-80	0-120	0-150
Fasted	3	59.6[b]	111.3	175.9	187.2
		(12.53)[a]	(26.67)	(13.46)	(16.82)
Fed	3	98.6	150.2	206.0	197.5
		(14.35)	(15.97)	(21.17)	(33.51)

[a]Standard deviation.

[b]Different from the fed group ($P < .025$).

in blood glucose were 187.2% for the fasted wethers and 197.5% for the fed wethers. Ikushima (1931) and Rothschild (1933) reported that the hyperglycemia caused by epinephrine was essentially dependent on the glycogen content of the liver. These data, obtained on the fasted and fed wethers, suggested that differences in liver glycogen were being measured. Shaw (1943) used the hyperglycemia following the intravenous injection of epinephrine as an index of the amount of liver glycogen in dairy cows.

No harmful side effects were observed in any of the epinephrine studies with sheep. An increased heart rate and frequent urinations were noticed. The frequent urinations can be explained by the hyperglycemia resulting in glycosuria.

Epinephrine Studies with Cattle

A preliminary report by Buchanan (1957) indicated that the dwarf and carrier cattle contained significantly less liver glycogen than pedigree-clean animals after they had been fasted for 72 hours. The epinephrine studies with fasted and fed sheep suggested the use of epinephrine as an indirect measure of liver glycogen in the dwarf and non-dwarf cattle.

Two Hereford heifers were each given a total dose of 0.75 c.c. epinephrine per 100 pounds of body weight. The dose was divided into three equal parts and injected at 20 minute intervals. In these and all other epinephrine injections which followed, the total dose of epinephrine was diluted to 10 c.c. with sterile saline prior to injection. The two heifers were extremely nervous before the test and struggled excessively during the test. The initial blood glucose values for the two heifers were 172.4 milligrams percent and 121.0 milligrams percent. These values

are some two to three times as high as those reported for cattle of this age. Epinephrine injections into the two heifers produced only a very slight rise in the blood glucose. Approximately 10 minutes after the third epinephrine injection, the heifer which had the highest initial glucose value collapsed and died after a few minutes of labored breathing. Upon autopsy a pulmonary edema was noted. The autopsy report concluded that most likely death was due to epinephrine toxicity. Sollmann (1948) lists the symptoms of epinephrine overdosage as anxiety, dyspnea, rapid pulse, high blood pressure, collapse, and death often in a few minutes. The toxic effects of epinephrine are due to acute cardiac dialation, pulmonary edema, ventricular fibrillation and these are most likely to occur if the heart is already weakened as a result of overexcitement or cardiac disease. He also states that some patients showed a hypersusceptibility to epinephrine, especially those of nervous temperament.

The dose level used on these heifers was one-half the maximum dose used with sheep on a body weight basis, and well below the maximum dose used on sheep calculated on the basis of body surface area. No ill effects had been noted with these levels in the wethers, however, none of the sheep had initial blood glucose levels which were abnormally high and they exhibited very little excitability. It appeared that the high initial glucose values of the two heifers were due to their extreme excitability. Dougherty et al. (1956) and Hodgson (1952) previously observed that excitement could cause an appreciable rise in the blood glucose of ruminants. The hyperglycemia has been attributed to an increased secretion of epinephrine from the adrenal medulla. The evidence indicated that the two heifers were highly stimulated before any exogenous epinephrine was administered.

Because of the possibility of detrimental effects of a large dose, later epinephrine injections in cattle were lowered to a single dose of 0.25 c.c. per 100 pounds of body weight. It was anticipated that this would reduce the harmful side effects of the hormone. Another consideration was the results obtained with the fasted and fed wethers which indicated that large differences in liver glycogen could be detected by a small dose.

In all tests, except those where young calves were used, animals with an initial blood glucose above 80 milligrams percent were eliminated from the tests. Approximately eight percent of the cattle tested were eliminated for this reason. Animals that had an initial blood glucose level of 80 milligrams percent or higher were usually very nervous and struggled considerably during the testing period. The results of the following tests are applicable under circumstances similar to those which have been described.

Non-Fasted Yearlings:

Four non-dwarf heifers, classified as three pedigree-clean and one known carrier, and four dwarfs of both sexes were injected intravenously with a single injection of 0.25 c.c. epinephrine per 100 pounds of body weight. The animals were of yearling age and were receiving a 50:50 roughage to concentrate ration. Blood samples were taken periodically for 90 minutes. Three of the non-dwarf heifers were from the purebred Angus herd at Stillwater. Blood samples from these animals were analyzed for glucose soon after they were obtained. The remaining animals were at Fort Reno and the samples from these animals were immediately placed in an ice water bath when collected. At the conclusion of the test, all blood tubes were packed in ice and brought to Stillwater for analysis.

The results of the intravenous injections of epinephrine in non-fasted dwarf and non-dwarf yearling cattle are recorded in tables V and VI. Table V shows the actual glucose values of the two groups, while table VI gives the percent changes at the various sampling intervals over the initial blood glucose level. The initial glucose values were 61.9 milligrams percent for the non-dwarfs and 64.6 milligrams percent for the dwarf animals. A peak hyperglycemia of 106.9 milligrams percent for the non-dwarfs occurred at 10 minutes following the epinephrine injection. The highest glucose value for the dwarf group, 87.7 milligrams percent, was observed 20 minutes after the epinephrine injection. Although the blood glucose values of the non-dwarf group were consistently higher at all sampling periods the differences between the two groups were not significantly different. Table VI shows that the percent increase in the blood glucose of the dwarfs was consistently lower at all sampling times. The percent increases five minutes after epinephrine were different ($P < .10$) for the dwarf and non-dwarf groups. The difference became greater ($P < .05$) 20 minutes following epinephrine, with percent increases at this sampling time of 69.7% for the non-dwarfs and 35.7% for the dwarf group. These results are supported by studies conducted by Massey (1958) in which the dwarfs showed only a slight increase in blood sugar after the injection of epinephrine. They reported that the response of the carrier and clean cows was considerably greater than the dwarf animals.

Fasted Yearlings:

Eight normal appearing yearling heifers, classified as four pedigree-cleans, two known carriers, and two which were questionable in regard to

TABLE V BLOOD GLUCOSE VALUES OF DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH EPINEPHRINE
(mg. per 100 ml. blood)

Group	Minutes After Epinephrine Injection					
	0	5	10	20	30	60
Non-Dwarf	61.9 (4)[b]	96.8 (2)	106.9 (3)	104.9 (4)	99.3 (3)	79.1 (3)
	(6.17)[a]	(15.34)	(15.28)	(13.54)	(16.79)	(7.53)
Dwarf	64.6 (4)		84.0 (4)	87.7 (4)	86.5 (4)	
	(10.29)		(22.42)	(19.83)	(17.73)	

[a]Standard deviation.

[b]Number of animals.

TABLE VI CHANGES IN THE BLOOD GLUCOSE OF DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH EPINEPHRINE

Group	Percent Increase from the Initial Glucose Value to the Various Sampling Times (in minutes)				
	0-5	0-10	0-20	0-30	0-60
Non-Dwarf	56.6[c] (2)[b]	65.7 (3)	69.7[d] (4)	53.6 (3)	33.1 (3)
	(21.64)[a]	(11.50)	(16.99)	(15.36)	(4.00)
Dwarf	29.7 (4)		35.7 (4)	34.1 (4)	
	(22.49)		(20.19)	(16.21)	

[a]Standard deviation.

[b]Number of animals.

[c]Different from the dwarf group ($P < .10$).

[d]Different from the dwarf group ($P < .05$).

their dwarfism status were fasted for 72 hours. After the fast they were injected intravenously with 0.25 c.c. epinephrine per 100 pounds of body weight. Two yearling dwarfs were also fasted and subjected to the same epinephrine dose. Most of the animals had been on pasture before the fast. Some of the same animals were later fed grain and hay rations before being subjected to the same treatment. Blood samples were taken at either 10 or 20 minute intervals during an 80 minute period. The samples were packed in ice and transported to Stillwater for analysis.

Tables VII and VIII show the blood glucose values and percent increases for the dwarf, carrier, questionable, and pedigree-clean yearling cattle. Although these data are limited, a few generalizations can be made. It appears that the type of ration the animal received prior to fasting had an effect on the response to epinephrine. The two carriers and one dwarf that received grass prior to the test also were tested after receiving grain and hay. When the carrier animals received grass prior to fasting, their blood glucose values prior to and 20 minutes after epinephrine were 44.8 and 66.4 milligrams percent respectively. This was an increase of 48.6 percent in the glucose content of the blood. When the same animals received hay and grain prior to fasting, the glucose values for the same sampling times were 50.5 and 92.2 milligrams percent. This was an increase of 83.0 percent, nearly twice the increase when the animals received a pre-fast ration of grass. The same trend was observed in the dwarf animals with the percent increases 20 minutes after epinephrine being 32.2% for dwarfs on grass and 57.2% for dwarfs in drylot. If the animals were storing more liver glycogen after receiving the drylot ration the increased hyperglycemia could be expected. Rats fed on a diet of oats reacted to

TABLE VII BLOOD GLUCOSE VALUES OF FASTED DWARF, CARRIER, AND PEDIGREE-CLEAN CATTLE INJECTED WITH EPINEPHRINE
(mg. per 100 ml. blood)

Pre-fast Ration and Genotype	No.	Minutes After Initial Epinephrine Injection						
		0	10	20	30	40	60	80
Grass								
Pedigree-clean	4	53.4 (9.25)[a]		81.2 (7.20)		89.2 (0.85)	87.0 (9.22)	86.4 (9.83)
Questionable[b]	2	54.2 (4.44)		74.6 (23.15)			69.7 (15.13)	70.4 (15.48)
Carrier	2	44.8 (0.92)		66.4 (4.03)		64.2 (4.45)	62.8 (5.23)	
Dwarf		37.2 (2)		46.0 (1)			52.8 (1)	39.6 (1)
Grain and Hay								
Carrier	2	50.5 (2.54)	96.7 (2.97)	92.2 (4.52)	89.5 (2.12)			
Dwarf	2	50.3 (8.20)		78.2 (2.26)		78.3 (5.51)	84.6 (11.03)	

[a]Standard deviation.

[b]Some of their near ancestors were carrier animals.

TABLE VIII CHANGES IN THE BLOOD GLUCOSE OF FASTED DWARF, CARRIER, AND PEDIGREE-CLEAN CATTLE INJECTED WITH EPINEPHRINE

Pre-fast Ration and Genotype	No.	Percent Increase from the Initial Glucose Value to the Various Sampling Times (in minutes)					
		0-10	0-20	0-30	0-40	0-60	0-80
Grass							
Pedigree-clean	4		52.5 (16.73)[a]		70.4 (8.06)	61.8 (16.51)	57.0 (25.38)
Questionable[b]	2		36.0 (30.05)			27.8 (14.58)	30.6 (17.32)
Carrier	2		48.6 (12.02)		43.5 (12.86)	40.5 (14.56)	
Dwarf	1		32.2			51.7	13.8
Grain and Hay							
Carrier	2	91.6 (3.74)	83.0 (18.17)	77.4 (4.73)			
Dwarf	2		57.2 (22.06)		56.8 (14.64)	68.6 (5.58)	

[a]Standard deviation.

[b]Some of their near ancestors were carrier animals.

epinephrine with a much more pronounced hyperglycemia than did rats fed on a diet of greens (Abderhalden and Wertheimer 1924). Although the authors did not make liver glycogen determinations, it would seem likely that differences in glycogen were being measured.

For those animals whose pre-fast ration was grass, their initial blood glucose values were 53.4, 54.2, 44.8, and 37.2 milligrams percent for the pedigree-clean, questionable, carrier, and dwarf animals respectively. Twenty minutes after epinephrine the respective increases for these same animals were 52.5, 36.0, 48.6, and 32.2 percent. The pedigree-clean animals had the highest blood glucose values at all the sampling times. The 60 minute increase for the carriers and the dwarf was 40.5% and 51.7%. The greater increase for the dwarf might be explained by the indications that the dwarf animals reached their peak hyperglycemia near 60 minutes while all of the non-dwarf animals exhibited their highest glucose values between 20 and 40 minutes after epinephrine. At 60 minutes the non-dwarf animals were showing a decline in their blood glucose. A percent increase of only 13.8 percent for the dwarf occurred 80 minutes after epinephrine. This is a more extreme decrease from the 60 minute value than the decrease shown by the non-dwarf animals.

Fasted Cows:

Twelve pedigree-clean and 10 known carrier mature cows, from Projects 650 and 873 respectively, were fasted for 72 hours prior to an intravenous injection of 0.25 c.c. epinephrine per 100 pounds of body weight. The cows were grazing native pasture prior to the fast and their calves had been weaned a few days before the test was conducted. Pre-fast blood

samples from eight pedigree-clean and six carrier cows were taken to determine the effect of the three day fast on the blood sugar level and to ascertain if any differences existed between the two groups of cows. Blood samples were taken at 20 and 60 minutes after epinephrine. The samples were handled as previously described.

Tables IX and X show the response of the pedigree-clean and carrier cows to the epinephrine injections. The pre-fast glucose values for the clean and carrier cows were 51.4 and 52.6 milligrams percent respectively. The decrease in blood glucose, after the 72 hour fast, was 9.9% for the pedigree-clean cows and 9.8% for the carrier cows. Twenty and 60 minutes after epinephrine the respective glucose increases for the clean cows were 45.5 and 82.4 percent. At the same sampling times the percent increases were 41.1 and 75.0 for the carrier cows. The pedigree-clean cows averaged slightly higher in both actual glucose values and percent increases. No significant differences existed between the two groups of cows. The two groups of fasted cows showed a smaller difference in the blood glucose response to epinephrine than the yearling pedigree-clean and carrier fasted animals. A possible age-response relationship may exist.

One cow from each group died approximately 24 hours after the test had been completed. Post mortem observations of the carrier cow showed dark spots occurring on the liver and kidneys. There was an edema of the brisket region and the stomachs contained a large amount of water. There were no indications that death was due to epinephrine toxicity. The pedigree-clean cow also exhibited post mortem findings similar to those of the carrier cow. These cows were approximately in their third month of pregnancy. A toxemia resulting from the fast could have been a

TABLE IX BLOOD GLUCOSE VALUES OF FASTED PEDIGREE-CLEAN AND KNOWN CARRIER COWS INJECTED WITH EPINEPHRINE
(mg. per 100 ml. blood)

Group	No.	Pre-fast	Minutes After Epinephrine 0	20	60
Clean	12	51.4 (8) (4.21)[a]	47.1 (6.82)	68.8 (16.53)	85.6 (20.01)
Carrier	10	52.6 (6)[b] (1.74)	45.8 (8.96)	63.7 (10.54)	78.8 (13.96)

[a]Standard deviation.

[b]Number of animals.

TABLE X CHANGES IN THE BLOOD GLUCOSE OF FASTED PEDIGREE-CLEAN AND KNOWN CARRIER COWS INJECTED WITH EPINEPHRINE

Group	No.	Decrease from Pre-fast to end of Fast	Percent Increase from the Initial Glucose Value to the Various Sampling Times (in minutes) 0-20	0-60
Clean	12	-9.9 (8) (9.15)[a]	45.5 (22.76)	82.4 (32.46)
Carrier	10	-9.8 (6)[b] (18.29)	41.1 (21.38)	75.0 (28.73)

[a]Standard deviation.

[b]Number of animals.

complicating factor. A number of yearling cattle were fasted at a later date with no harmful effects. The yearlings were allowed their fill on hay before going back into the drylot. The cows that died were among a group that were placed on pasture immediately following the test.

Tranquillized, Fasted Yearlings:

It was soon observed that the temperament and excitability of the animal could greatly influence the blood sugar level. Animals that were wild and those which offered considerable resistance to the testing procedure usually showed a one to two fold increase in blood glucose. The use of a tranquillizer offered a possibility of controlling the temperament of animals being tested.

Six yearling heifers were divided into two equal groups following a three day fast. Each group contained two pedigree-clean heifers and one known carrier heifer. Blood samples were obtained before the animals were placed on the fast. After the fasting period, one group of heifers was injected intravenously with 0.3 milligram of chlorpromazine[1] per pound of body weight. Forty minutes after the injection of the tranquillizer all six of the heifers were injected intravenously with 0.25 c.c. epinephrine per 100 pounds of body weight. The blood was sampled at 20 and 60 minutes after epinephrine and was handled as previously described.

The results of the injection of the tranquillizer into the three fasted heifers and the response of the six heifers to the epinephrine are shown in tables XI and XII. From these data one cannot tell whether

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[1] Trade name - Thorazine HCL. Each milliliter contained 25 milligrams chlorpromazine hydrochloride with two percent benzyl alchol as preservative. Manufactured by Smith, Kline, and French Laboratories. Philadelphia, Pennsylvania.

TABLE XI EFFECT OF CHLORPROMAZINE ON THE BLOOD GLUCOSE OF FASTED HEIFERS, BEFORE AND AFTER EPINEPHRINE
(mg. per 100 ml. blood)

Group	No.	Pre-fast	Before Chlor-promazine	Before Epin-ephrine	Minutes After Epinephrine 20	60
Chlorpromazine	3	65.4 (4.59)[a]	64.9 (6.91)	69.1[b] (1.65)	88.0[b] (12.35)	97.1[c] (0.14)
Control	3	59.8 (2.31)		49.8[d] (5.88)	68.6 (7.81)	70.1 (6.94)

[a]Standard deviation.

[b]Different from the control group ($P < .10$).

[c]Different from the control group ($P < .005$).

[d]Different from the pre-fast control mean ($P < .10$).

TABLE XII CHANGES IN THE BLOOD GLUCOSE OF FASTED HEIFERS INJECTED WITH CHLORPROMAZINE AND EPINEPHRINE

Group	No.	Decrease from Pre-fast to the End of Fast	Percent Increase in Epinephrine	
			0-20	0-60
Chlorpromazine	3	-0.9[b] (3.68)[a]	35.5 (11.60)	42.7 (11.31)
Control	3	-16.6 (9.73)	38.1 (12.64)	41.0 (10.96)

[a]Standard deviation.

[b]Different from the control group ($P < .10$).

the chlorpromazine was effective in controlling blood glucose levels in excitable animals because the initial levels of the injected animals were within the normal range. The pre-fast glucose values for the chlorpromazine and control groups were 65.4 and 59.8 milligrams percent respectively. After the three day fast the blood glucose of the chlorpromazine group had decreased only 0.9 percent, while the blood glucose level of the control group had decreased 16.6 percent. The discrepancy between the two groups was probably due either to sampling errors or that the effect of handling and the temperament of the chlorpromazine treated group masked the fasting effect. Forty minutes after the chlorpromazine injection there was an average increase in the blood glucose of approximately five milligrams percent. One of the heifers did not show an increase. Norman and Hiestand (1955) reported that the intra-peritoneal injection of chlorpromazine into fed or fasted mice and hampsters resulted in a hyperglycemia. The hyperglycemia in the mice and hampsters was quite noticable 30 minutes after chlorpromazine, but much greater three hours after the injection. There was no noticable change in the blood glucose of rats even though extremely large doses of chlorpromazine were given.

Decourt (1953) stated that one of the actions of chlorpromazine was an adrenergic blocking agent. Adrenaline blocking is a rather vague term because it does not specify whether it is the production, release, or the effects after the release that is inhibited. The data obtained on the yearling heifers indicated that the action of epinephrine on liver glycogen was not inhibited by intravenous chlorpromazine. Sixty minutes after the epinephrine injection the blood glucose values were 97.1 and 70.1 milligrams percent for the chlorpromazine and control heifers

respectively. The difference between the two groups was highly significant ($P < .005$). Probably the greater part of the observed difference was due to the fact that the chlorpromazine injected heifers had a higher blood glucose following fasting in addition to the slight increase following chlorpromazine. When the glucose values following epinephrine were expressed as a percent of the initial glucose value, the means of the two groups were very similar. Sixty minutes after epinephrine the percent increases for the chlorpromazine and control groups were 42.7 and 41.0 respectively.

The outward reaction of the heifers to the intravenous injection of chlorpromazine did not prove satisfactory. One heifer, which was quite docile at the beginning of the test, was tranquillized to the stage of not being able to stand. Another heifer, which was quite nervous at the start of the test, did not lose her sense of fear and struggled constantly throughout the testing period. Her actions were incoordinated and it appeared that injury could easily occur.

Glucose Tolerance

The intravenous glucose tolerance curve of blood sugar constitutes a rapid test for the efficiency of the glucose-regulating mechanism of the body. The original belief that glucose tolerance was determined primarily by a relative increase in insulin secretion by the pancreas, in response to the hyperglycemia produced by the administered sugar, has been shown to be false (Soskin et al. 1934). These workers have demonstrated that glucose tolerance depends primarily upon the homeostatic mechanism of the liver. This mechanism is affected physiologically by the endocrine

balance and other factors existent at the time of the test. Glucose tolerance tests were conducted on dwarf and non-dwarf animals to evaluate the glucose-regulating efficiency of the two groups.

Non-fasted:

Seven non-dwarf and six dwarf animals, with both sexes and both Angus and Hereford breeds being represented, were utilized for this test. All animals were yearlings or a few months older. The animals were from Project 873 and were maintained on a 50:50 roughage to concentrate ration. The non-dwarfs received three pounds, the dwarfs two pounds of this ration per 100 pounds body weight. A 50 percent glucose[1] solution was injected intravenously via the left jugular vein so that each animal received 0.5 gram per kilogram of body weight. The glucose was infused through a 15 gauge needle as rapidly as possible. The injection time varied from five to nine minutes with the majority of the animals receiving all the glucose in a five minute period. An initial blood sample was taken before the glucose infusion and subsequent blood samples were taken through a three hour period after glucose administration. All of the blood samples, except the initial, were taken from the right jugular vein. This precautionary measure was used to prevent the blood samples from being contaminated with glucose from the area where the glucose was injected. The protein was removed from some of the samples at Fort Reno. These filtrates were quick frozen with dry ice and returned to Stillwater for analysis. The protein was removed from the remainder of the samples at Stillwater and the filtrates were frozen immediately. The samples were analyzed from one to three weeks later.

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[1]Dextrose Anhydrous Merck, U.S.P.

Tables XIII and XIV show the results of the glucose tolerance tests. Figure 1 presents the tolerance curves for the dwarf and non-dwarf groups. The initial blood glucose levels were 70.7 milligrams percent for the non-dwarfs and 55.2 milligrams percent for the dwarfs. The difference between the means was significant ($P < .05$). Except for the five minute sample the non-dwarf group had higher blood glucose values throughout the three hour sampling period. Five minutes after glucose infusion the glucose level of the blood of the dwarfs increased 409.0% over the initial value which was considerably higher ($P < .10$) than the 238.5% increase in the blood glucose shown by the non-dwarf group. The dwarfs tended to show a slightly less tolerance for glucose as evidenced by the slower rate of return of their blood glucose to the initial level. The percent increases, 30 minutes after glucose infusion were 108.0% and 158.0% for the non-dwarf and dwarf groups respectively. For the same respective groups the percent increases three hours after glucose infusion were 10.0% and 35.3%.

Fasted:

Six non-dwarf and seven dwarf yearling animals were subjected to the glucose tolerance test as described above for the non-fasted animals, with the exception that they were fasted three days previous to the test. A number of animals were common to both phases of the glucose tolerance tests. The animals were held in dry lot with free access to water. The blood samples were handled in the same manner except that the protein was removed from part of the samples at Fort Reno. These samples were refrigerated overnight, then brought to Stillwater in a portable cooler and

TABLE XIII BLOOD GLUCOSE VALUES OF NON-FASTED AND FASTED DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH GLUCOSE
(mg. per 100 ml. blood)

Group	No.	Initial	Minutes Following Glucose Infusion 5	30	60	120	180
Non-Fasted							
Non-Dwarf	7	70.7 (5.52)[a]	237.9 (57.71)	146.1 (18.74)	118.9 (15.11)	87.6 (13.77)	77.8 (16.56)
Dwarf	6	55.2[b] (16.62)	259.1 (54.48)	135.1 (32.67)	97.7 (32.59)	74.8 (33.04)	71.5 (17.35)
Fasted							
Non-Dwarf	6	66.5 (7.75)	341.1[c] (62.18)	208.1[c] (23.30)	156.2 (9.51)	132.5 (13.69)	114.9 (12.04)
Dwarf	7	62.5 (7.79)	278.3 (54.92)	187.6 (11.04)	156.4 (10.21)	135.1 (11.78)	114.1 (12.22)

[a]Standard deviation.

[b]Different from the non-fasted non-dwarf group ($P < .05$).

[c]Different from the fasted dwarf group ($P < .10$).

TABLE XIV CHANGES IN THE BLOOD GLUCOSE OF NON-FASTED AND FASTED DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH GLUCOSE

Group	No.	Percent Increase from the Initial Glucose Value to the Various Sampling Times (in minutes)				
		0-5	0-30	0-60	0-120	0-180
Non-Fasted						
Non-Dwarf	7	238.5[b] (84.74)	108.0 (34.07)	68.9 (25.08)	24.2 (20.43)	10.0 (21.17)
Dwarf	6	409.0 (195.40)[a]	158.0 (75.23)	79.8 (39.12)	46.6 (42.06)	35.3 (40.14)
Fasted						
Non-Dwarf	6	422.3 (133.58)	218.3 (63.59)	138.4 (37.41)	102.0 (34.53)	75.3 (31.81)
Dwarf	7	347.5 (82.54)	204.1 (40.01)	154.2 (39.72)	120.3 (41.47)	85.4 (33.87)

[a]Standard deviation.

[b]Different from the non-fasted dwarf group ($P < .10$).

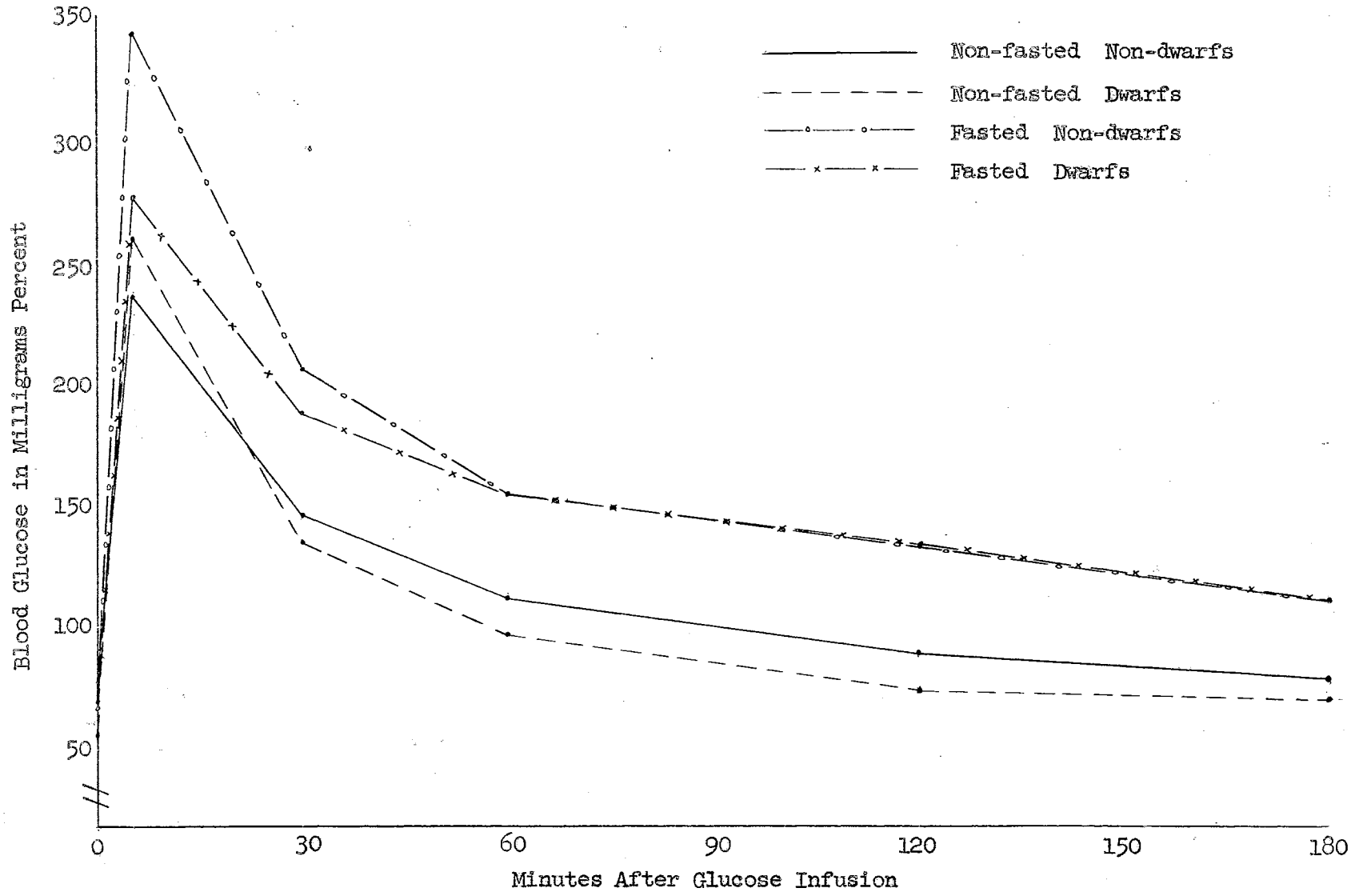

Figure 1. Glucose Tolerance Curves of Fasted and Non-Fasted Dwarf and Non-Dwarf Yearling Cattle

frozen. The protein was precipitated from the remainder of the samples at Stillwater, and the filtrates were immediately frozen.

Tables XIII and XIV show the results of the glucose tolerance tests with the fasted non-dwarf and dwarf yearling cattle. Figure 1 presents the tolerance curves for the two groups. The initial glucose values were 66.5 milligrams percent for the non-dwarfs and 62.5 milligrams percent for the dwarf animals. Five minutes and 30 minutes following the glucose infusion the glucose content of the blood was higher ($P < .10$) in the non-dwarf animals than in the dwarfs. Five minutes after the glucose infusion the blood glucose values were 341.1 and 278.3 milligrams percent for the non-dwarf and dwarf groups respectively. Thirty minutes after the glucose injection the blood glucose level was 208.1 milligrams percent for the non-dwarfs and 187.6 milligrams percent for the dwarfs. At the remaining three sampling times the glucose values of the two groups were essentially the same. Three hours after glucose infusion the glucose values were 114.9 and 114.1 milligrams percent for the non-dwarf and dwarf groups respectively. The five minute blood glucose increases were 422.3% for the non-dwarfs and 347.5% for the dwarfs. This was the reverse of the response obtained under non-fasting conditions. The same trend was observed in that the dwarfs did not tolerate glucose as well as the non-dwarf group. Two hours after the infusion of glucose the percent increase for the non-dwarf group was 102.0 while 120.3 was the percent increase for the dwarfs.

Fasting the animals for three days decreased their tolerance for glucose considerably. Both the dwarf and non-dwarf groups had higher blood glucose values and percent increases when given glucose following

the fasting period. Three hours after glucose infusion the percent increases were 10.0 and 75.3 for the non-fasted non-dwarfs and fasted non-dwarfs respectively. The respective increases were 35.3 and 85.4 percent for the non-fasted dwarfs and the fasted dwarfs. This is typical of the other sampling times and demonstrates the decreased tolerance for glucose as a result of fasting the animals. Chambers (1938) in reviewing the effect of fasting on glucose tolerance stated that all species studied have reacted similarly in that they showed a decreased tolerance for glucose after short fasting periods. Holmes (1951) reported that cows showed a decreased tolerance for glucose after they had been fasted for 48 hours. McCandless et al. (1948) observed a decreased glucose tolerance in fasted sheep. The reason for the decreased tolerance is not known, however, a number of theories have been proposed. Comprehensive experiments by Cori and Cori (1928a) established that glucose administered to fasted rats was oxidized at a slower rate. A theory was advanced that hunger diabetes resulted from the failure of the islet tissue of the pancreas to secrete insulin in the absence of ingested carbohydrate. Such a theory was supported by the experiments of Best et al. (1939), which showed that the insulin content of the pancreas of fasted or fat-fed rats was less than that of normally fed rats. This might explain the decreased tolerance for glucose after fasting.

Originally the maximal amount of sugar that could be taken orally on an empty stomach, in man or animals, without glycosuria was spoken of as the assimilation limit or tolerance for that sugar. The height of the blood sugar rise and its rate of return to the normal glycemic level following an intravenous injection of glucose or other sugar are better

indices of the sugar tolerance of an animal than those obtained by the oral administration method. In mature ruminants the intravenous method for glucose tolerance is the only one which will give significant results. Oral administrations of glucose to mature ruminants produces little change in the blood sugar level (Kennedy et al. 1939 and Bell and Jones 1945).

In this study the variation between the individual tolerance curves was quite large. The most variation existed at the peak hyperglycemia measured five minutes after the infusion of the glucose. At this sampling time the ranges for the non-fasted animals were from 118.4 to 383.9 milligrams percent, while for the fasted animals the ranges were 156.4 to 711.5 milligrams percent. Both the dwarf and non-dwarf groups were equally as variable. The glucose tolerance curves for the dwarf and non-dwarf animals were quite similar and showed that the glucose utilization was not impaired to any great extent. These results agree with those of Weaver et al. (1957) who concluded that the dwarfs were not lacking in ability to lower their blood sugar to the pre-injection level after glucose administration.

Insulin Tolerance

Results obtained by Foley et al. (1956) indicated that dwarf beef cattle were highly sensitive to insulin injections because of their difficulty in returning their glucose to pre-injection levels following insulin. This information stimulated the initiation of insulin tolerance tests with dwarf and non-dwarf cattle.

Non-fasted:

Eleven non-dwarf and nine dwarf yearling animals from both the Angus and Hereford breeds were subjected to insulin tolerance tests. The experimental groups consisted of five bulls and 15 heifers. Most of the animals used in this test had been used previously in the glucose tolerance studies, which were conducted one to two months previous to this time. Insulin[1] was injected intravenously at the rate of 0.36 unit per pound of body weight. Blood samples were obtained over a six hour period after the injection. The criteria measured were the depth of hypoglycemia and the blood glucose return to pre-injection levels.

The results are presented in tables XV and XVI. The tolerance curves for the dwarf and non-dwarf groups are shown in figure 2. The initial glucose values were 60.4 milligrams percent for the non-dwarfs and 60.7 milligrams percent for the dwarf group. One-half hour and one hour after insulin the non-dwarf group showed larger decreases in the glucose content of the blood than did the dwarfs. At these respective sampling times the percent decreases for the non-dwarf group were 60.6 and 60.0, while for the dwarfs the percent decreases were 54.2 and 48.9. None of these differences were significant. Six hours after insulin the blood glucose of the non-dwarf animals was significantly ($P < .025$) higher than the dwarfs. At this sampling time the respective glucose values for the non-dwarf and dwarf groups were 54.7 and 43.0 milligrams percent. When these values were expressed as percent decreases from the initial glucose level the non-dwarfs were 3.8% below initial values, while the dwarfs were 30.3% below their initial blood glucose level. The difference between the two

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[1]U-40 Iletin (Insulin, Lilly), U.S.P. Eli Lilly and Co. Indianapolis, Indiana.

TABLE XV BLOOD GLUCOSE VALUES OF DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH INSULIN
(mg. per 100 ml. blood)

Group	Hours After Insulin					
	0	.5	1	2	4	6
Non-Dwarf	60.4 (11) (7.97)[a]	24.0 (2)[b] (5.05)	25.0 (4) (3.29)	28.8 (11) (6.30)	35.1 (5) (9.37)	57.4[c] (11) (10.11)
Dwarf	60.7 (9) (9.94)	30.9 (3) (3.71)	29.9 (2) (2.54)	29.8 (9) (6.35)	32.2 (4) (3.58)	43.0 (9) (14.80)

[a]Standard deviation.

[b]Number of animals.

[c]Different from the dwarf group ($P < .025$).

TABLE XVI CHANGES IN THE BLOOD GLUCOSE OF DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH INSULIN

Group	Percent Decrease from the Initial Glucose Value to the Various Sampling Times (in hours)				
	0-.5	0-1	0-2	0-4	0-6
Non-Dwarf	60.6 (2) (5.57)[a]	60.0 (4)[b] (7.17)	51.7 (11) (10.26)	37.9 (5) (19.14)	3.8[c] (11) (12.13)
Dwarf	54.2 (3) (2.29)	48.9 (2) (13.71)	50.6 (9) (9.87)	41.6 (4) (8.42)	30.3 (9) (14.78)

[a] Standard deviation.

[b] Number of animals.

[c] Different from the dwarf group ($P < .001$).

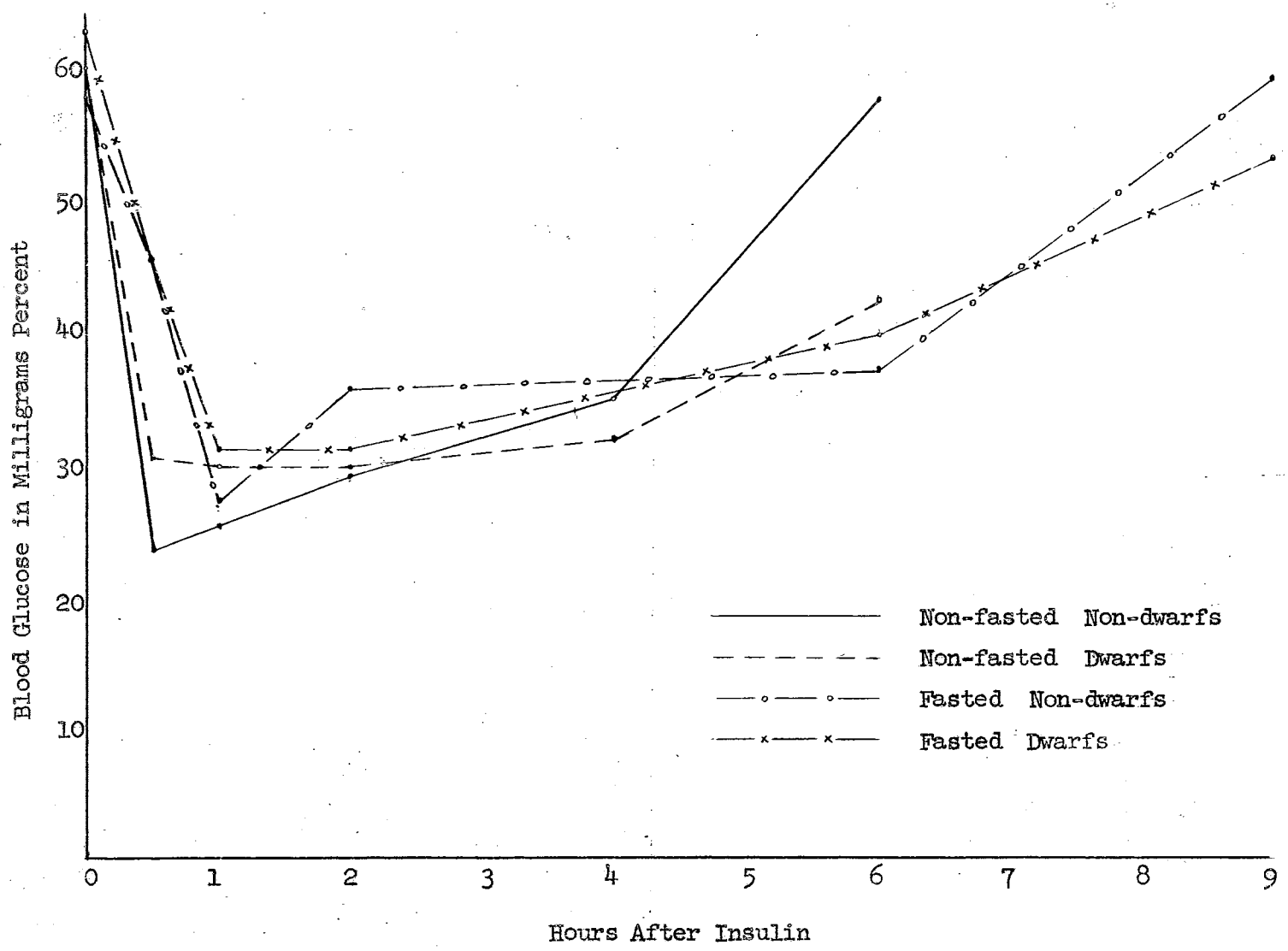

Figure 2. Insulin Tolerance Curves of Fasted and Non-Fasted Dwarf and Non-Dwarf Yearling Cattle

groups was highly significant ($P < .001$), indicating that the non-fasted dwarfs were more sensitive to the insulin in that they required a longer time to return their blood glucose to the pre-injection level. This agrees with the results obtained by Foley et al. (1956) and Massey (1958). However, they reported that the blood sugar of the dwarfs dropped more rapidly and to a lower level than the blood glucose of the normal appearing animals. Results of this study were in disagreement with their findings. One-half hour after insulin a minimum mean glucose value of 24.0 milligrams percent resulted for the non-dwarfs while for the dwarf group the lowest mean glucose level was 29.8 milligrams percent, occurring two hours after the insulin injection. The Missouri workers were testing cows, while yearlings were used in this study. The disagreement may therefore be due to an age effect.

The lowest glucose value obtained, after the insulin injection, was 20.2 milligrams percent with the majority of the lower glucose values occurring below 28.0 milligrams percent. No noticeable harmful effects were observed as a result of the insulin injections. Symptoms of insulin shock are rare in ruminants, and it is only after the blood glucose has been lowered to extremely low levels for long periods of time that any convulsive signs are observed (Reid 1951b).

In a review concerning the mechanism of insulin action, Haugaard and Marsh (1953) concluded that the primary physiologic effect of insulin in lowering the blood sugar was brought about by its action in increasing the utilization (oxidation and storage) of glucose in the organs and tissues of the body. Decreasing the net production of glucose by the liver may be important also.

Fasted:

Seven non-dwarf and eight dwarf yearling cattle were subjected to the same treatment as described above for the non-fasted cattle with the exception that they were fasted for three days. Nearly all of these animals were the same as those utilized in the non-fasted insulin test. The blood was sampled over a nine hour period.

Tables XVII and XVIII show the response of the yearling cattle to the intravenous injections of insulin after they had been fasted. The tolerance curves of these two groups are presented in figure 2. The initial blood glucose values for the non-dwarf and dwarf groups were 58.0 and 63.4 milligrams percent respectively. The blood glucose values for the two groups were very similar at all sampling times. The non-dwarf group was slightly lower at one hour and higher at nine hours following insulin. The values for the non-dwarfs at these respective sampling times were 26.9 and 59.0 milligrams percent. For the same respective sampling times the values for the dwarf group were 31.1 and 52.8 milligrams percent. The maximum percent decrease for the dwarfs was 53.4 at two hours following insulin, whereas the largest decrease for the non-dwarfs was 47.4 which occurred one hour after insulin. Nine hours after insulin, the non-dwarf group was 15.7 percent above their initial glucose level, while the dwarfs were 9.9 percent below their pre-injection level. It is well established that the injection of insulin causes an increased secretion of epinephrine. It is therefore understandable how some of the animals returned their blood glucose to levels higher than their initial values.

TABLE XVII. BLOOD GLUCOSE VALUES OF FASTED DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH INSULIN
(mg. per 100 ml. blood)

Group	Hours After Insulin					
	0	.5	1	2	6	9
Non-Dwarf	58.0 (7) (8.16)[a]	46.0 (4) (10.21)	26.9 (3) (3.51)	35.8 (4) (11.11)	37.6 (7) (5.56)	59.0 (3) (14.69)
Dwarf	63.4 (8)[b] (4.67)	46.3 (5) (4.64)	31.1 (3) (3.23)	31.0 (5) (5.50)	39.7 (8) (8.63)	52.8 (3) (25.25)

[a]Standard deviation.

[b]Number of animals.

TABLE XVIII CHANGES IN THE BLOOD GLUCOSE OF FASTED DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH INSULIN

Group	Percent Decrease from the Initial Glucose Value to the Various Sampling Times (in Hours)				
	0-.5	0-1	0-2	0-6	0-9
Non-Dwarf	26.9 (4) (11.55)[a]	47.4 (3) (8.99)	42.6 (4) (14.18)	34.1 (7) (11.97)	+15.7 (3) (35.79)
Dwarf	30.0 (5)[b] (7.55)	43.3 (2) (4.95)	53.4 (5) (6.74)	36.4 (8) (14.79)	9.9 (3) (42.78)

[a]Standard deviation.

[b]Number of animals.

Fasting influenced the return of the blood glucose to pre-injection levels in the non-dwarf animals. The response of the dwarfs, six hours after insulin, was similar both under fasted and non-fasted conditions. Six hours after insulin the percent decreases for the fasted and non-fasted non-dwarfs were 34.1 and 3.8 respectively. For the same sampling times the respective percent decreases were 36.1 and 30.3 for the fasted and non-fasted dwarfs. Six hours after insulin the difference between the fasted non-dwarf and dwarf groups was small and not significant. Thus, fasting had abolished the significant differences which had resulted before the two groups were fasted. A possible explanation for this is not known. It is possible that larger differences between the two groups could have been found by sampling the blood between six and nine hours after insulin.

One Angus heifer, which was quite excitable, had an initial glucose value of 82.3 milligrams percent. One-half hour after insulin, instead of the blood glucose decreasing it had increased to 128.9 milligrams percent. However, six hours after insulin the glucose value was 45.3 milligrams percent which was comparable to the blood glucose values for the other non-dwarf animals. This demonstrated the antagonistic action of epinephrine over insulin. Wishnofsky et al. (1944) reported that epinephrine could completely neutralize the action of insulin administered intravenously or subcutaneously.

During one phase of the tests with the fasted animals, an extremely rapid drop in the temperature occurred on the day the test was conducted. One hour after the insulin injection all three of the dwarf animals exhibited marked muscular tremors which lasted for approximately one-half hour. The three non-dwarf animals did not show any unusual reactions.

The observed sensitivity of the dwarfs was probably due to the combination of the three day fast, cold weather, and the insulin injection.

Effect of Insulin on Blood Glucose Compartments:

Additional observations were made on eight of the fasted animals that were used in the trial described above. The same treatment was imposed. Hematocrit readings were made on the initial blood sample. Both the initial blood sample and the sample taken one-half hour after insulin were analyzed for plasma glucose. Corpuscular glucose was estimated using the following formulas reported by Laris (1958).

plasma glucose conc. expressed as mg./100 c.c. plasma	x	the fraction of whole blood that is plasma	=	mg. glucose in the plasma of the 100 c.c. whole blood system

mg. glucose in 100 c.c. whole blood	-	mg. glucose located in plasma of the 100 c.c. whole blood system	=	mg. glucose in the red cells of the 100 c.c. whole blood system

The purposes of this experimental phase were to determine what effect insulin had on the glucose of the various blood compartments and if any differences were evident between the non-dwarf and dwarf groups.

The results are shown in table XIX. The whole blood glucose is the sum of the glucose contained in the plasma and the corpuscles. The initial glucose values of the various blood glucose compartments for the fasted non-dwarf and dwarf groups were as follows: whole blood glucose, 63.0 and 65.8 milligrams percent; plasma glucose, 51.8 and 54.5 milligrams percent; and corpuscular glucose, 11.2 and 11.3 milligrams percent. The differences between the two groups were very small and not significant. One-half hour after the insulin injection the values for the whole

TABLE XIX GLUCOSE CONTENT OF VARIOUS BLOOD COMPARTMENTS OF FASTED DWARF AND NON-DWARF YEARLING CATTLE INJECTED WITH INSULIN
(mg. per 100 ml. blood)

	Non-Dwarf	Dwarf
Initial		
Whole Blood	63.0 (4)[b] (8.50)	65.8 (4) (3.22)
Plasma[a]	51.8 (4) (2.74)[c]	54.5 (4) (10.41)
Corpuscular	11.2 (4) (7.22)	11.3 (4) (7.36)
.5 Hour After Insulin		
Whole Blood	41.2 (3) (4.33)	47.0 (4) (5.07)
Plasma[a]	33.4 (3) (4.40)	38.7 (4) (5.11)
Corpuscular	7.9 (3) (4.71)	8.2 (4) (2.33)

[a]Glucose content of the plasma of a 100 milliliter whole blood system.

[b]Number of animals.

[c]Standard deviation.

blood and plasma glucose were 41.2 and 33.4 milligrams percent for the non-dwarfs, while 47.0 and 38.7 milligrams percent were the values for the dwarfs. The corpuscular levels of glucose following insulin were 7.9 and 8.2 milligrams percent for the non-dwarf and dwarf groups respectively. Insulin decreased the glucose in all three of the blood glucose compartments and the size of the decreases were quite similar for the three compartments. The validity of the corpuscular glucose values are questionable. Following centrifugation some of the plasma samples showed varying degrees of red color indicating that some hemolysis had occurred. Also, Behrendt (1957) stated that centrifugation may introduce an analytical error, because it favors the initiation of glycolysis.

Blood Glucose Values of Young Calves

Whole blood, plasma, and corpuscular glucose values were obtained on seventeen calves, approximately one month of age. Hematocrit values were also determined. The calves were divided into three groups consisting of ten probable cleans, six known carriers, and one dwarf. All the calves, except the dwarf were from Project 670 and were of both sexes. The dwarf was from Project 873. Both the Angus and Hereford breeds were represented. The blood samples were collected at Fort Reno and the protein was immediately precipitated from the blood. The filtrates were refrigerated overnight, then transported to Stillwater and frozen.

The results are presented in table XX. For the probable clean calves the glucose values for the whole blood, plasma, and corpuscles were 96.8, 68.5, and 28.3 milligrams percent respectively. For the known carrier calves the glucose values for the same respective glucose compartments

TABLE XX WHOLE BLOOD, PLASMA, AND CORPUSCULAR GLUCOSE VALUES OF ONE-MONTH-OLD CALVES
(mg. per 100 ml. blood)

Group	No.	Whole Blood	Plasma	Corpuscular	Hematocrit
Probable Clean	10	96.8 (11.84)[a]	68.5 (11.17)	28.3 (5.20)	39.7 (3.08)
Known Carrier	6	100.5 (15.03)	71.9 (14.37)	28.8 (5)[b] (4.90)	37.4 (5) (4.79)
Dwarf	1	40.1	30.1	10.0	38.5

[a]Standard deviation.

[b]Number of animals.

were 100.5, 71.9, and 28.8 milligrams percent. The differences between the clean and carrier groups were not significant. The glucose values for the one dwarf were considerably lower and resemble more closely the values obtained for yearling cattle (table XIX). None of the pedigree-clean or known carrier calves had glucose values which were near those of the dwarf. It was unfortunate that more dwarf calves were not available for this comparison.

The data in tables XIX and XX clearly show the effect of age on the glucose content of the blood of cattle. For the one-month-old calves the whole blood glucose is approximately 100 milligrams percent, while 60 milligrams percent is the approximate amount of whole blood in the yearlings. The corpuscular glucose values were approximately 28 milligrams percent for the calves and approximately 11 milligrams percent for the yearlings. This represents a sizeable decrease in the glucose content of the corpuscles which can be attributed to age.

An Estimate of the Variation Encountered From Duplicate Blood Glucose Determinations

Most procedures for chemical analyses suggest that samples be analyzed in duplicate. The basis for the duplicate determinations is to reduce sampling errors and variations in the analytical procedure. Very little information exists as to the fraction of the total variation that is contributed by differences in the duplicate determinations.

In this study all glucose determinations were made in duplicate. Therefore, data were available to estimate the percent of the total variation that could be accounted for by the variation between duplicates. The animals were divided into three age groups because the variation in the

blood glucose values varied between age groups. The age groups consisted of one-month-old calves, yearlings, and mature cows. The number of animals in each group were 16, 62, and 21 respectively. Only initial blood glucose values were used. Both clean and carrier animals were included in the study. The blood samples were re-analyzed if there was an error greater than 10 percent between the optical density readings of the duplicates. None of the blood samples of the cows or calves required re-analysis. In the yearlings, samples from seven animals were re-analyzed. Therefore, in the yearling cattle the variation between duplicates would be reduced.

An analysis of variance, as described by Snedecor (1956), was used to separate the known sources of variation. The amount of variation for each source was calculated from the estimated mean squares (tables XXXI, XXXXII, and XXXIII). Variation between duplicates accounted for 13.6, 12.5, and 8.6 percent of the total variation for the calves, yearlings, and cows respectively. Only a small part of the total variation between the blood glucose values was accounted for by the variation between duplicates, with the majority of the variation existing between animals. Although the variation between duplicates was quite small, duplicate analysis would still be recommended. Duplicate determinations permits a very good check against the occurrence of gross errors which otherwise would remain undetected. This would be especially beneficial where small differences in blood glucose were being measured.

Repeatibility of Blood Glucose Determinations

Two pre-test glucose values were available on each of 38 yearling cattle of the Hereford and Angus breeds. Both sexes were represented. The second glucose sample was obtained one to two months following the first sample. The environmental conditions at the time of the second sample were very similar to those when the first sample was obtained. The estimate of the repeatibility of blood glucose was calculated by the method of least squares.

The estimate of repeatibility was .29. This estimate was quite low and indicated that many of the animals' second glucose value differed quite widely from the first value. One may question the repeatibility of the blood glucose levels of samples taken a few minutes apart on the same animal, however, limited observations would indicate the repeatibility to be high.

If the repeatibility of blood glucose is as low as has been found in this study (.29), the repeatibility of tests using blood glucose as a primary test criteria may be low also. The validity of repeated tests measuring small differences in blood glucose would be questionable. The percent change in the blood glucose of the same animal subjected to the same test at different time periods may be similar if the change in blood glucose is not influenced by the initial glucose level. Observations on the blood glucose values of different animals indicated that the initial glucose level, if in the normal range, had little, if any influence on the percent change in blood glucose. However, when the initial glucose level was extremely high, as a result of the animal's temperament, the

percent change from the initial value was usually smaller than with animals whose initial glucose values were within the normal range. Exceptions to this were noted in the glucose tolerance studies.

General Discussion

The response of dwarf and non-dwarf cattle to intravenous injections of epinephrine, glucose, and insulin permit some interesting comparisons. The dwarfs were more sensitive to insulin than the non-dwarf animals in that they were slower in returning their blood glucose to pre-injection levels. de Bodo et al. (1952b) and Kosaka (1954) demonstrated that hypophysectomized and adrenalectomized dogs were more sensitive to insulin than normal dogs. The dogs which had these glands removed required a much longer period of time to return their blood glucose to pre-injection levels following insulin. ACTH, cortisone, or growth hormone abolished the insulin hypersensitivity of the dogs (de Bodo et al. 1950 and 1952a). The insulin hypersensitivity of hypophysectomized animals has never been satisfactorily explained. Any factor or a combination of factors may be involved, namely defective gluconeogenesis, impaired glycogen mobilization, retarded inactivation of insulin or increased sugar utilization. Thus, an agent which is capable of modifying the insulin hypersensitivity of hypophysectomized animals may act on any one or any combination of these factors.

de Bodo et al. (1952b) concluded that the adrenalectomized dog was more sensitive to insulin than the normal dog, but less sensitive than the hypophysectomized dog. This was true as long as the adrenalectomized dog, whether with or without DCA maintenance, was still well nourished

and tested only in the post-absorptive state. They also concluded that the adrenal cortical atrophy was an important factor in the production of the insulin hypersensitivity of the hypophysectomized dog. However, the absence of an anterior pituitary factor (other than ACTH) was also of great importance in the production of this metabolic abnormality.

The dwarf animals showed a smaller epinephrine hyperglycemia than the non-dwarfs. This was evident under both fasted and non-fasted conditions. Evidence was presented earlier which indicated the possibility of using epinephrine hyperglycemia as an index of liver glycogen. If such an index is valid then it would be assumed that both the fasted and non-fasted dwarf animals had less liver glycogen than the non-dwarf animals which were subjected to the same treatment. This conclusion would be partly supported by Buchanan (1957), where dwarf and carrier animals had significantly less liver glycogen than pedigree-clean animals. These animals had been fasted for 72 hours and liver glycogen was analyzed directly from liver samples. However, Buchanan found that the differences in liver glycogen were non-existent when the tests were conducted with fed cattle. Thus, a discrepancy exists between liver glycogen estimated by epinephrine hyperglycemia and actual liver glycogen levels.

de Bodo et al. (1942) observed only a slight hyperglycemia after the intravenous injection of epinephrine into hypophysectomized dogs. Normal dogs responded with a marked hyperglycemia. These workers showed that the hypophysectomized dog had amounts of liver glycogen which were adequate to have produced marked hyperglycemia had they been available. Some of these dogs had normal amounts of liver glycogen, and even those with the smallest amounts were within the range of liver glycogen found

in fasted normal animals which showed a far greater hyperglycemia after epinephrine. Wide ranges of glycogen levels were observed in the hypophysectomized dogs but the hyperglycemia response to epinephrine had absolutely no relation to the liver glycogen levels. It was concluded that there was a definite impairment in the mobilization of liver glycogen when the hypophysectomized dogs were injected with epinephrine.

The epinephrine hyperglycemia of the dwarf animals compares favorably with the epinephrine hyperglycemia of the hypophysectomized dogs. Differences in epinephrine hyperglycemia may reflect differences in liver glycogen in normal animals. However, the results reported by de Bodo et al. (1942) pointed out conclusively that this may not hold true in some cases of endocrine dysfunctions. These workers are among the very few who have correlated known amounts of liver glycogen with the epinephrine hyperglycemia.

Long et al. (1942) reported that adrenalectomized and hypophysectomized animals, in contrast to normal animals, undergo a rapid decline in liver glycogen when subjected to periods of fasting. Increased carbohydrate oxidation appears to be the cause of the rapid loss of glycogen. These results could explain the differences in the liver glycogen levels of fasted dwarf and non-dwarf cattle obtained by Buchanan (1957) and the lack of liver glycogen differences in the fed cattle could be justified by the experiments of Soskin et al. (1935). These workers observed that both adrenalectomized and hypophysectomized dogs were able to maintain normal liver glycogen levels provided they were fed adequately. If the dwarf animals respond similarly to the adrenalectomized and hypophysectomized animals reported above, then these results and those of Buchanan (1957) are not inconsistent.

de Bodo et al. (1950) reported that the response of untreated hypophysectomized dogs to intravenous glucose was similar to that seen in normal dogs, except that there was always a marked hypoglycemic phase following the initial period of hyperglycemia. In this study, the response of the dwarf animals to the injection of glucose was similar to that of the non-dwarfs. The hypoglycemic phase was not observed possibly because the sampling period was terminated before the animals had reached their pre-injection levels.

The dwarf animals in this study responded quite similarly to the reported responses of the hypophysectomized and adrenalectomized dogs but not to such an extreme degree. These comparisons suggest that the dwarf may be deficient in pituitary or adrenal hormones or that these hormones are present but unable to function properly in the regulation of carbohydrate metabolism.

Some of the non-dwarf animals used in this study were known carriers. X-ray classification, based on the radiographic examination of the lumbar vertebrae, were available on all the non-dwarf yearling animals. Most of the animals used in the glucose tolerance and insulin tolerance studies were classified in the B x-ray type. This would suggest that only a few animals free of dwarfism were included in the non-dwarf groups. The blood glucose differences obtained between the dwarf and non-dwarf animals could be expected to be approaching a minimum. This would be true if carrier animals responded similarly to dwarfs and differently from animals free of dwarfism.

The variation in the glucose content of the blood was found to be very large. The known sources of variation are numerous. Many others

are suspected, while others probably exist undetected. One of the known sources of variation which can vary the blood glucose tremendously is the temperament and excitability of the animal. This factor has been reported by only a few workers as a source of variation. The reason for this appears to be that most of the experimental animals had been handled considerably and extreme variations in temperament did not exist. Variations in temperament can easily mask the effects of the treatments imposed and make the probability of determining differences very small. In this study, the elimination of animals with initial glucose values higher than 80 milligrams percent probably only removed some of the more excitable animals. Many animals could have had large increases in blood glucose, as a result of excitement, and still have had initial values in the normal range.

If further blood glucose studies were to be conducted, it would appear necessary to attempt to eliminate the variation caused by excitement. One possible means would be to select docile animals and handle them considerably before conducting the tests. This type of experimental material would be useful only in elucidating the more fundamental aspects of the physiology of dwarfism and not to develop a diagnostic test to be applied to the cattle population. However, such information may eventually provide the basis for developing a diagnostic test for dwarfism.

SUMMARY AND CONCLUSIONS

Sixty-five non-dwarf and 17 dwarf cattle of the Hereford and Angus breeds were subjected to tests designed to measure differences in carbohydrate metabolism. Many of the same animals were common to the various tests. The cattle were injected intravenously, in separate tests, with epinephrine, insulin, and glucose. In all tests, blood glucose was the response measured. Preliminary studies were conducted with yearling western wethers to obtain information on epinephrine dosage levels to provide information for the epinephrine studies with cattle. The findings of this study were as follows:

(1) Epinephrine studies with sheep demonstrated that large increases in blood glucose could result from periodic injections of epinephrine. There appeared to be a maximum effective epinephrine dose, which if exceeded at any one injection would cause little, if any, additional change in the blood glucose level.

(2) The larger epinephrine hyperglycemia of fed sheep, as compared to fasted sheep, suggested that differences in liver glycogen could be measured.

(3) Epinephrine doses much smaller than the maximum dose used on sheep could not be tolerated by cattle.

(4) Epinephrine hyperglycemic differences between fasted pedigree-clean and known carrier cows were very small. Dwarfs responded

to epinephrine injections with smaller increases in blood glucose than non-dwarf animals. This response was evident in both fasted and non-fasted animals. The epinephrine hyperglycemia was smaller in animals with a pre-fast ration of grass as compared to a pre-fast ration of grain and hay.

(5) Glucose tolerance curves were similar for the dwarf and non-dwarf groups. Animals which were fasted three days prior to glucose injections showed a decreased tolerance for glucose.

(6) Dwarf animals were more sensitive to insulin injections in that they were slower in returning their blood glucose to pre-injection levels. Six hours after insulin, when the glucose values were expressed as a percent change from the initial value, the difference between the dwarf and non-dwarf groups was highly significant. A three day fast abolished the significant difference which had existed before the two groups were fasted.

(7) Only small differences were observed between pedigree-clean and known carrier calves for whole blood, plasma, and corpuscular glucose. Observations on one dwarf calf revealed considerably smaller values.

(8) The animal's temperament was observed to have a profound influence on the glucose content of the blood. A tranquillizer, Chlorpromazine, was not satisfactory in controlling excitement.

(9) Only a small part of the total variation in blood glucose was accounted for by the variation between duplicate determinations.

A repeatibility estimate for the blood glucose of yearling cattle was found to be .29.

(10) The dwarf animals in this study responded quite similarly to the reported responses of hypophysectomized and adrenalectomized dogs but not to such an extreme degree. These comparisons suggest that the dwarf may be deficient in pituitary or adrenal hormones or that these hormones are present but unable to function properly in the regulation of carbohydrate metabolism.

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A P P E N D I X

TABLE XXI BLOOD GLUCOSE VALUES OF YEARLING WESTERN WETHERS INJECTED WITH EPINEPHRINE
(Glucose in mg. percent)

Treatment	Wether No.	Minutes After Initial Epinephrine Injection										
		0	5	10	20	30	40	50	60	80	100	120
I	10	63.4	103.3	103.3	107.8	107.8						
	3	59.7	82.6	90.5	100.4	98.3						
II	2	71.6	88.4	92.6	108.3	108.7						
	5	67.9	82.2	91.3	98.8	94.6						
III	4	74.2		90.5	103.9	110.3						
	0	67.1		93.0	104.1	114.9	116.5					
IV	5	45.8			74.2		82.4		80.8			
	4	41.6			79.6		83.2		81.2			
V	10	40.4			58.4		87.6		87.6			
	0	51.6			87.6		109.5		112.4			
VI	2	46.2			70.0		82.6		95.0			
	3	56.2			76.2		103.3		127.3			
VII	10	57.9			114.0		129.3		160.7	182.2	204.1	213.6
	4	57.5			89.7		115.3		141.3	153.3	163.2	179.3
VIII	0	68.8			108.7		142.1		157.0	156.6		
	3	60.0			100.0		126.0		157.0	140.5		
IX	5	59.2		94.6	115.3	131.8	140.5	148.8	162.8			
	7	49.6		72.3	95.0	103.3	103.7	123.1	138.0			

TABLE XXII BLOOD GLUCOSE VALUES OF FASTED AND NON-FASTED YEARLING WESTERN WETHERS INJECTED WITH EPINEPHRINE[a]

Condition	Wether No.	Minutes after Initial Epinephrine Injection				
		0	40	80	120	150
Fasted	5	53.0	78.7	100.4	143.8	146.2
	7	40.0	63.4	82.0	106.6	112.4
	3	52.9	91.3	127.3	154.1	162.0
Fed	4	65.8	140.1	169.0	206.2	187.6
	10	63.8	126.8	169.0	205.8	214.0
	0	68.4	126.0	156.6	193.0	186.0

[a]Epinephrine dosage: each wether received 1.5 c.c., divided into six equal parts and injected at 20 minute intervals.

TABLE XXIII BLOOD GLUCOSE VALUES OF FASTED YEARLING HEIFERS INJECTED WITH CHLORPROMAZINE[a] AND EPINEPHRINE[b]
(Glucose in mg. percent)

Group	Animal No.	Genotype	Breed	Pre-fast	Before Chlor-promazine	Before Epin-ephrine	Minutes After Epinephrine 20	60
Tranquillized	OK 7-80	Clean	Hereford	61.2	58.2	68.6	73.8	
	OK 7-31	Clean	Hereford	70.3	72.0	70.9	94.4	97.0
	T785	Carrier	AXH CB	64.6	64.5	67.7	95.9	97.2
Control	T775	Carrier	AXH CB	61.2		44.6	67.5	62.1
	OK 7-89	Clean	Hereford	61.0		56.2	76.9	73.7
	OK 7-67	Clean	Hereford	57.1		48.7	61.4	74.4

[a]The chlorpromazine treated animals each received 0.3 milligrams per pound of body weight.

[b]Each animal received 0.25 c.c. per 100 pounds of body weight.

TABLE XXIV BLOOD GLUCOSE VALUES OF YEARLING CATTLE INJECTED WITH EPINEPHRINE[a]
(Glucose in mg. percent)

Group	Animal No.	Breed	Sex	Fasted or Non-Fasted	Minutes after Initial Epinephrine Injection								
					0	5	10	20	30	40	60	80	90
Non-dwarf	683	Angus	F	NF	54.6			103.3		93.1	71.2		
	633	Angus	F	NF	62.6	107.6	103.6	97.9	97.2		86.2		
	715	Angus	F	NF	60.8	85.9	93.8	94.0	83.6		79.8		75.0
Carrier	T794	AXH CB	F	NF	160.5		202.9	189.6	190.9				
	T785	AXH CB	F	NF	69.6		123.4	124.4	117.0				
Dwarf	T661	Hereford	M	NF	65.4		70.6	71.5	72.5				
	T690	Hereford	M	NF	58.8		91.6	92.0	87.0				
	T90	Hereford	F	NF	55.4		63.2	73.3	75.8				
	T757	Angus	F	NF	78.7		110.8	114.0	110.8				
Clean	OK7-06	Hereford	F	F	53.8			89.2		88.6	91.2		
	OK7-18	Hereford	F	F	51.0			78.5		89.8	91.1		
	OK7-01	Hereford	F	F	86.6			107.3			133.6	141.9	
	OK7-20	Hereford	F	F	45.4			73.4			73.2	79.4	
	OK7-58	Hereford	F	F	67.1			86.2			92.5	93.3	
Quest.	OK7-25	Hereford	F	F	58.2			91.5			80.4	83.1	
	OK7-35	Hereford	F	F	94.1			108.8			104.4	106.1	
	OK7-92	Hereford	F	F	50.2			57.6			59.0	59.4	
Carrier	T775[b]	AXH CB	F	F	48.7		94.6	95.4	88.0				
	T785[b]	AXH CB	F	F	52.3		98.8	89.0	91.0				
	T785	AXH CB	F	F	44.1			69.3		67.3	66.5		
	T775	AXH CB	F	F	45.4			63.6		61.0	59.1		
Dwarf	T90[b]	Hereford	F	F	56.1			79.8		82.2	92.4		
	D100[b]	Angus	F	F	44.5			76.6		74.4	76.8		
	T90	Hereford	F	F	34.8			46.0			52.8	39.6	
	D100	Angus	F	F	39.6								

[a]Each animal received 0.25 c.c. per 100 pounds of body weight.

[b]These animals received grain and hay prior to the fast. The other fasted animals were previously on pasture.

TABLE XXV BLOOD GLUCOSE VALUES OF FASTED MATURE HEREFORD COWS INJECTED WITH EPINEPHRINE[a]
(Glucose in mg. percent)

Group	Cow No.	Pre-fast	Minutes after Epinephrine 0	20	60
Clean	11	54.1	45.5	60.2	64.6
	56	56.2	55.2	75.2	92.9
	19	55.2	54.2	65.8	74.8
	12	52.0	43.1	58.9	71.6
	3	48.8	46.0	75.7	87.7
	57	49.0	51.1	65.5	83.2
	31	52.4	40.4	58.4	83.0
	25	43.3	35.3	42.0	79.1
	43[b]		45.6	60.0	70.5
	58		40.3	67.3	77.6
	13		50.2	93.6	101.5
	41		58.0	103.5	140.3
Carrier	T49	55.2	53.2	67.2	90.1
	T86[b]	52.4	45.3	60.5	92.6
	T46	52.8	64.6	73.3	75.6
	T68	53.5	48.0	55.0	69.4
	T64	52.1	39.0	58.4	70.6
	T60	49.9	35.6	43.6	62.3
	T20		36.7	61.4	61.0
	T62		38.0	63.1	76.7
	T141		48.9	79.6	103.9
	T80		48.2	74.6	85.8

[a]Each cow received 0.25 c.c. per 100 pounds of body weight.

[b]These two cows died approximately 24 hours following the completion of the test.

TABLE XXVI BLOOD GLUCOSE VALUES OF NON-FASTED YEARLING CATTLE INJECTED WITH INSULIN[a]
(Glucose in mg. percent)

Group	Animal No.	Breed	Sex	Hours After Insulin					
				0	.5	1	2	4	6
Non-dwarf	T812	Angus	F	57.8	20.5		30.6		61.2
	T848	Angus	F	63.8	27.6		40.6		78.7
	T808	Angus	M	47.5			23.6	24.9	46.8
	T824	Angus	M	53.6			21.6	40.4	53.6
	T804	Angus	M	75.3			22.6	24.8	40.5
	T800	Angus	F	58.4			32.7	42.0	47.9
	915	Angus	F	55.5			23.2	43.2	55.7
	OK7-06	Hereford	F	62.6		23.8	24.4		63.0
	OK7-18	Hereford	F	71.4		22.2	29.8		65.8
	T785	AXH CB	F	62.6		29.9	37.0		62.4
	T775	AXH CB	F	55.5		24.0	30.7		56.1
Dwarf	T773	AXH CB	F	60.8	26.5		31.4		44.8
	T897	Angus	F	70.9	31.7		35.0		57.8
	T896	Angus	F	70.6	34.2		38.8		56.7
	T898	Angus	M	55.7			25.2	30.0	28.0
	T846	Hereford	M	58.2			29.6	28.4	27.3
	T869	Hereford	F	53.6			21.4	34.2	33.6
	T757	Angus	F	54.0			20.2	36.1	34.0
	D100	Angus	F	76.0		31.7	34.2		68.7
	T90	Hereford	F	46.2		28.1	32.8		36.3

[a]Each animal received 36 units per 100 pounds of body weight.

TABLE XXVII BLOOD GLUCOSE VALUES OF FASTED YEARLING CATTLE INJECTED WITH INSULIN[a]
(Glucose in mg. percent)

Group	Animal No.	Breed	Sex	Hours After Insulin					
				0	.5	1	2	6	9
Non-dwarf	T808	Angus	M	65.6	38.2		25.1	31.1	
	T824	Angus	M	64.9	46.2		35.8	41.6	
	T804	Angus	M	50.8	39.3		35.2	34.4	
	T800	Angus	F	70.6	60.4		47.3	45.7	
	915	Angus	F	54.1		27.9		32.2	44.1
	T812	Angus	F	52.0		23.0		36.6	59.6
	T848	Angus	F	48.0		29.8		41.8	73.4
	T805	Angus	F	82.3	128.9		88.0	45.3	
Dwarf	T846	Hereford	M	66.2	45.0		25.2	29.8	
	T898	Angus	M	70.2	49.6		40.0	49.6	
	T869	Hereford	F	63.4	52.4		29.4	45.6	
	T757	Angus	F	63.4	40.9		29.0	39.8	
	T899	Hereford	F	68.0	43.6		31.2	38.0	
	T773	AXH CB	F	59.6		27.5		24.8	24.6
	T896	Angus	F	60.5		32.2		47.1	73.4
	T897	Angus	F	56.0		33.7		43.0	60.3

[a]Each animal received 36 units per 100 pounds of body weight.

TABLE XXVIII EFFECT OF INSULIN[a] ON THE BLOOD GLUCOSE COMPARTMENTS OF FASTED YEARLING CATTLE
(Glucose expressed in mg. percent)

Group	Animal No.	Hematocrit	Hours after Insulin 0 Plasma	0 Corpuscular	.5 Plasma	.5 Corpuscular
Non-Dwarf	T808	31.4	79.1	11.3	41.4	9.8
	T824	32.4	79.6	11.1	46.2	11.3
	T804	31.2	70.7	2.3	53.7	2.5
	T800	38.6	82.5	20.0		
Dwarf	T846	28.7	72.4	14.6	55.8	5.2
	T898	30.1	100.0	0.3	60.0	7.7
	T869	33.1	72.6	14.8	62.8	10.4
	T757	33.0	71.4	15.6	46.6	9.7
	T899	34.0				

[a]Each animal received 36 units per 100 pounds of body weight.

TABLE XXIX GLUCOSE[a] TOLERANCE TESTS WITH YEARLING CATTLE
(Glucose expressed in mg. percent)

Group	Animal No.	Fasted or Non-Fasted	Initial	Minutes after Glucose Infusion 5	30	60	120	180
Non-dwarf	T802[b]	NF	77.0	244.6	155.4	128.4	86.0	76.2
	915	NF	78.7	161.7	139.9	116.2	102.8	102.6
	T805	NF	102.8	383.9	297.6	222.5	119.4	113.8
	T848	NF	72.1	298.9	125.6	133.6	95.5	89.0
	T812	NF	64.7	225.0	174.4	137.2	93.4	80.4
	T808	NF	83.4	118.4	103.0	76.0	72.8	84.3
	T824	NF	65.1	198.0	134.2	116.8	97.4	82.4
	T804	NF	67.7	210.5	129.1	98.7	71.9	60.8
	T800	NF	69.6	326.8	164.3	101.3	66.0	53.6
Dwarf	T898	NF	39.7	301.8	114.6	65.9	15.6	40.1
	T047[b]	NF	91.8	314.2	173.4	138.8	152.6	142.9
	T846	NF	61.4	286.6	176.9	145.0	98.9	74.4
	T773	NF	31.9	236.3	120.0	70.0	64.0	68.0
	T896	NF	80.4	171.7	101.5	99.4	100.0	105.2
	T897	NF	71.8	271.0	147.7	116.0	101.5	80.4
	T899	NF	72.2	299.5	161.8	116.4	97.8	91.8
	T789	NF	54.2	159.5	89.6	73.0	71.0	74.4
Non-dwarf	915	F	68.0	382.2	224.5	166.6	139.2	109.2
	T848	F	57.8	408.8	220.2	156.4	119.2	110.2
	T812	F	58.6	368.6	234.0	168.5	147.4	129.6
	T808	F	68.1	239.2	169.2	147.8	127.8	101.6
	T824	F	79.0	350.0	199.4	145.9	115.4	108.0
	T800	F	67.5	298.2	201.8	152.2	145.9	130.6
	T805	F	151.6	711.5	378.4	339.9	200.3	170.3
Dwarf	T898	F	53.8	296.5	181.6	148.6	127.4	103.2
	T846	F	68.5	301.8	184.8	162.8	126.3	117.2
	T773	F	61.4	318.7	209.3	163.1	132.8	98.6
	T896	F	69.4	213.9	176.6	153.7	139.4	122.2
	T897	F	51.2	197.6	179.1	161.1	149.6	126.8
	T899	F	71.2	348.2	190.2	138.2	120.0	103.2
	T869	F	61.9	271.9	191.8	167.3	150.4	127.6
	T757	F	84.9	156.4	153.4	146.3	127.8	111.2
	T018[c]	F	134.0	426.8	313.4	259.2	199.8	163.0

[a]Each animal received 0.5 gm. per kilogram of body weight.

[b]Angus male.

[c]Hereford female.

TABLE XXX GLUCOSE CONTENT OF BLOOD COMPARTMENTS OF ONE-MONTH-OLD CALVES
(Glucose expressed in mg. percent)

Group	Calf No.	Breed	Sex	Whole Blood Glucose	Plasma Glucose	Corpuscular Glucose	Hematocrit
Clean	289	Angus	M	99.0	65.7	33.3	43.0
	259	Angus	F	110.2	77.8	32.4	39.0
	OK 9-10	Hereford	M	98.6	65.6	33.0	40.0
	339	Angus	M	108.8	83.8	25.0	38.0
	269	Angus	M	83.6	49.6	34.0	46.0
	OK 9-06	Hereford	F	80.4	54.3	26.1	39.5
	329	Angus	M	115.8	83.6	32.2	35.0
	OK 9-04	Hereford	F	89.6	68.0	21.6	37.5
	OK 9-40	Hereford	F	89.2	68.3	20.9	38.0
	049	Angus	F	92.6	68.4	24.2	41.0
Carrier	OK 9-11	Hereford	M	83.0	52.2	30.8	45.0
	OK 9-13	Hereford	F	99.4			
	OK 9-28	Hereford	M	103.0	78.1	24.9	32.0
	OK 9-43	Hereford	F	91.8	67.4	24.4	38.0
	OK 9-46	Hereford	M	98.0	70.4	27.6	36.0
	OK 9-53	Hereford	M	127.6	91.3	36.3	36.0
Dwarf	T927	Hereford	M	40.1	30.1	10.0	38.5

TABLE XXXI ANALYSIS OF VARIANCE FOR INITIAL BLOOD GLUCOSE OF HEREFORD COWS

Source	d.f.	Mean Squares	Component Expectation	Component Estimates
Total	41			
Cows	20	138.55	$\sigma D^2 + 2\sigma C^2$	67.76
Determinations	21	3.04	σD^2	3.04

TABLE XXXII ANALYSIS OF VARIANCE FOR INITIAL BLOOD GLUCOSE OF YEARLING CATTLE

Source	d.f.	Mean Squares	Component Expectation	Component Estimates
Total	123			
Animals	61	223.77	$\sigma D^2 + 2\sigma A^2$	108.26
Determinations	62	7.24	σD^2	7.24

TABLE XXXIII ANALYSIS OF VARIANCE FOR INITIAL BLOOD GLUCOSE OF ONE-MONTH-OLD CALVES

Source	d.f.	Mean Squares	Component Expectation	Component Estimates
Total	31			
Animals	15	326.38	$\sigma D^2 + 2\sigma C^2$	157.46
Determinations	16	11.45	σD^2	11.45

VITA

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Candidate for the Degree of

Doctor of Philosophy

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