Endocrine Characteristics of a Miniature Condition in Brahman Cattle: Circulating Concentrations of Some Growth-Related Hormones (43281)

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Abstract. **Four miniature Brahman calves born in 1988 and 1989, along with four contemporary sex-matched Brahman control calves, were used in experiments to determine circulating concentrations of insulin-like growth factor I (IGF-I), growth hormone (GH), insulin, triiodothyronine, and thyroxine, and plasma glucose response to insulin challenge. The effect of plane of nutrition on plasma concentrations of IGF-I and insulin was also determined and a clinical screen of blood chemistries was conducted to determine effects of calf type. Plasma IGF-I was six times higher in control calves compared with miniature calves (209.0 vs 35.0 ng/ml; $P = 0.001$). However, miniature calves had mean plasma GH about six times higher (37.8 vs 6.2 ng/ml; $P = 0.004$) and had twice as many secretory episodes (9 vs 4.5; $P = 0.005$) over an 8-hr sampling period. Plasma concentrations of triiodothyronine (2.54 vs 1.80 ng/ml) and thyroxine (88.8 vs 56.2 ng/ml) were higher in control compared with miniature calves ($P = 0.001$), but concentrations of triiodothyronine and thyroxine in both calf types were within normal ranges. Although miniature calves displayed similar plasma glucose concentrations to controls, hypoglycemic response to insulin challenge tended to be greater in miniature calves. Nutritional regulation of circulating IGF-I appeared to be intact in miniature as well as control calves, as evidenced by a reduction in plasma IGF-I concentration following a decrease in plane of nutrition, and a subsequent increase in plasma IGF-I concentration following realimentation. Serum urea nitrogen was lower ($P = 0.02$) in control compared with miniature calves. These data describe a miniature condition in Brahman cattle that is manifested by apparently normal proportioned growth but small stature, and that is associated most notably with abnormally low circulating concentrations of IGF-I in the presence of paradoxically high circulating concentrations of GH. This condition appears to be similar to Laron dwarfism in humans, in which the low IGF-I is caused by an abnormality in the GH receptor.** [P.S.E.B.M. 1991, Vol 197]

With current national emphasis being placed on the need for efficient production systems for lean meat, it is necessary to understand genetic, nutritional, and physiological mechanisms involved in the regulation of growth and protein accretion in food-producing animals. Historically, knowledge of biological systems often has been developed by studying perturbed biological systems or by studying naturally occurring animal models of altered metabolism. A miniature condition in Brahman cattle observed in our herd appears to be characterized by normally proportioned growth, but small stature, and presents an opportunity to study regulation of growth in an economically important species of food-producing animals. Of specific interest is the systematic evaluation of hormonal patterns and regulatory mechanisms that may be involved in aberrant growth patterns.

Two paternal half-sibling miniature Brahman cattle, one bull and one heifer, were born in 1985 at the Subtropical Agricultural Research Station, Brooksville, FL (1). Their dams were paternal half sisters, and their

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Received November 26, 1990. [P.S.E.B.M. 1991, Vol 197]
Accepted April 24, 1991.

0037-9727/91/1974-0450$3.00/0

dams had a common maternal grandam (Fig. 1). At 18 months of age, the body weight (343 kg) and hip height (115 cm) of the bull were 3.7 and 4.9 SD, respectively, less than the mean of its small-to-medium frame male Brahman contemporaries. The heifer at 18 months of age had body weight (222 kg) and hip height (111 cm) that were 3.1 and 2.8 SD, respectively, less than its small-frame female Brahman contemporaries. In 1988, the miniature female produced a miniature heifer calf sired by the miniature bull. In 1989, the miniature female and two of her paternal half-sisters produced miniature bull calves sired by the miniature bull. Both years, the miniature bull also was bred to other related cows with the aim of producing animals that would express the miniature gene(s). Miniature calves born in 1988 and 1989, along with contemporary controls, were used in experiments to determine circulating concentrations of insulin-like growth factor I (IGF-I), growth hormone (GH), insulin, triiodothyronine (T_3), and thyroxine (T_4).

Materials and Methods

Animals. In July 1988, three half-sibling Brahman heifers (88–44, 88–298, and 88–369) sired by the miniature bull (85–440) and three Brahman control heifers (88–255, 88–371, and 88–374) were weaned onto a 12% crude protein preconditioning diet (Bingo Pre-Conditioning Pellets—Medicated; Lakeland Cash Feed Co., Inc., Lakeland, FL). The dam of 88–44 was the 1985 miniature female (85–166). Age at weaning ranged from 3.5 to 7.5 months. This preconditioning diet was replaced by the fifth week after weaning with a complete mixed diet of 67.5% corn, 20% cottonseed hulls, and 12.5% of a 52.0% crude protein, vitamin, and mineral premix with monensin (Custom Beef Concentrate 52 Pellets—Medicated, Lakeland). Heifers were fed individually in individual pens, and water was available at all times. Feed was offered once daily (2 PM) at 2.2% of body weight, following 4 hr together as a group in an exercise yard. Feed refusals were collected daily. Dry-matter content of feed and feed refusals were determined by drying to constant weight and actual feed intake calculated on a dry-matter basis. Heifers were weighed weekly and feed offered was adjusted weekly.

In August 1989, three half-sibling miniature Brahman bull calves (89–240, 89–321, and 89–411) sired by 85–440 and three contemporary control Brahman bull calves (89–189, 89–328, and 89–403) were weaned and handled as described for the 1988 heifer calves. Age at weaning ranged from 5 to 7 months. The dam of 89–411 was 85–166. For the purpose of selecting calves for the miniature condition, two blood samples were obtained 1 week apart and stored frozen for analysis of IGF-I and GH. All bull calves selected to represent the miniature calf type had birth weights less than 22.5 kg, and relatively low plasma IGF-I (<80 ng/ml) associated with relatively high plasma GH (>30 ng/ml). Control bull calves were selected that had birth dates within 9 days of each of the miniature calves. Control calves had a common sire (83–357).

Experiments. During each of the 2 years, a series of similar experiments were conducted beginning 6 weeks after weaning. Initially, blood samples were obtained by venipuncture on five consecutive days at 10 AM each day. Blood was collected in polypropylene tubes (Monovette; Sarstedt, Inc., Princeton, NJ) containing EDTA and centrifuged. Plasma was collected and stored at −20°C in polypropylene vials for analysis of IGF-I, T_3, and T_4. Data were evaluated by analysis of variance for effects of calf type (miniature or normal-stature controls) using a randomized complete block design (2).

As a separate experiment, blood samples were collected every 10 min for 8 hr via indwelling jugular cannulae into polypropylene tubes. Plasma was obtained and stored at −20°C for analysis of GH. Mean concentration of GH, peak frequency, and peak amplitude were determined using PULSAR (3) with peak identification criteria set by the method of Elsasser *et al.* (4). Effect of calf type on each of these variables was determined by simple one-way analysis of variance (2).

Another experiment was conducted to measure the responsiveness of IGF-I to changing plane of nutrition. Plasma concentrations of insulin were also monitored during this experiment. Blood samples were obtained on Days 1, 4, 8, 12, and 13. Feed offered was reduced by 50%, to 1.1% of body weight, for 1 week and blood samples were obtained daily (Days 14, 15, 16, 17, 18, 19, and 20). The level of feeding was restored to 2.2% of body weight and blood was sampled daily for an additional 5 (1988) or 6 (1989) days (Days 21, 22, 23, 24, 25, and 26). All blood samples were obtained at 10 AM by venipuncture and plasma was stored, as described above, for analysis of IGF-I and insulin. Data were analyzed as a split-plot, with calf type (miniature or normal) and feeding period as the main plots and blood-sampling day of each feeding period as the subplot using the GLM Procedure of SAS (2). Single degree of freedom contrasts were used to evaluate linear and quadratic effects of period. On Days 8, 12, 24, and 26 of the second year (bull calves only), additional blood samples were collected to screen 24 serum chemistries and ratios (enzymes, minerals, electrolytes, and metabolites). These analyses were performed commercially (Doctors and Physicians Laboratory, Leesburg, FL). These data were analyzed for effects of calf type using a randomized complete block design (2).

During the second year (bull calves only), hypoglycemic response to insulin challenge was tested. Bovine insulin (Sigma Chemical Co., St. Louis, MO), in 40% polyethylene glycol 8000 (w/v; Sigma), was adminis-

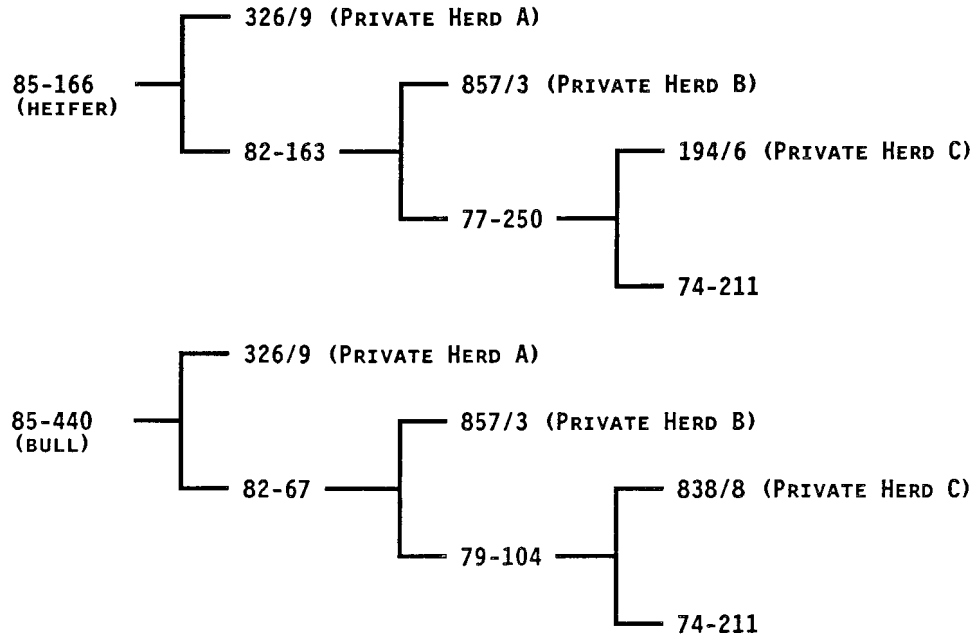

Figure 1. Partial pedigree of two paternal half-sibling miniature Brahman cattle, one bull and one heifer, born in 1985. All miniature calves in this study were sired by this bull (85–440). Dams of the miniature calves used were this female (85–166) and two of her paternal half-sisters.

Table I. Effect of Calf Type on Plasma Insulin-Like Growth Factor I, Triiodothyronine, and Thyroxine

Hormone (ng/ml)	Calf type		SE	*P*
	Miniature ($n = 4$)	Control ($n = 4$)		
IGF-I	35.0	209.0	2.4	0.001
T_3	1.80	2.54	0.06	0.001
T_4	56.2	88.8	1.5	0.001

tered intramuscularly at the rate of 0.045 mg insulin/kg body $wt^{.75}$. Blood samples were obtained by jugular venipuncture at 0, 2, 6, 12, 18, and 24 hr after insulin administration. Plasma was obtained as described previously and stored at −20°C for analysis of insulin and glucose. Glucose was determined by an automated method (Industrial Method 339–19; Technicon Industrial Systems, Tarrytown, NY) based on the glucose oxidase procedure described by Gochman and Schmitz (5). Effect of calf type on plasma insulin and glucose at each sampling time and area under the respective insulin and glucose response curves were analyzed by simple one-way analysis of variance (2).

Hormone Assays. Plasma IGF-I was measured by a double-antibody radioimmunoassay based on the glycyl-glycine acidification procedure described by Underwood *et al.* (6) and modified and validated for bovine plasma by Elsasser *et al.* (4). Additional details of this assay are given by Hammond *et al.* (7). Intraassay and interassay coefficients of variation for IGF-I were 8.4% and 10.0%, respectively. Plasma concentrations of T_3 and T_4 were measured by solid-phase radioimmunoassay using commercial kit assays (ICN, Immunochem, Inc., Costa Mesa, CA) as described previously (8) and validated for use with bovine plasma (7). All samples across each phase of the study were analyzed for T_3 and T_4 in one assay in order to eliminate interassay variation. Intraassay coefficients of variation were 3.2% for T_3 and 5.8% for T_4. Plasma concentrations of insulin were measured by double-antibody radioimmunoassay as described previously (9). Intraassay and interassay coefficients of variation for insulin were 5.0% and 8.0%, respectively. Plasma GH was measured by double-antibody radioimmunoassay using antiserum and methods described by Elsasser *et al.* (10). Intraassay and interassay coefficients of variation for GH were 7.5% and 12.0%, respectively.

Results

Assuming that the miniature condition was controlled by a single autosomal recessive gene, the only 1988 calf known to express the miniature condition was 88–44, a daughter of miniature parents, 85–440 and 85–166. Based on early phenotypic appearance and related pedigrees, 88–298 and 88–369 were only suspect miniature calves sired by the miniature bull and from dams that were the bull's paternal half sisters. One calf in 1988 (88–44) had circulating hormone concentrations uncharacteristic of the other five calves. The most notable differences were relatively low plasma IGF-I associated with relatively high GH. As described in Materials and Methods, this endocrine condition was used to screen 1989 calves for use in the second year's

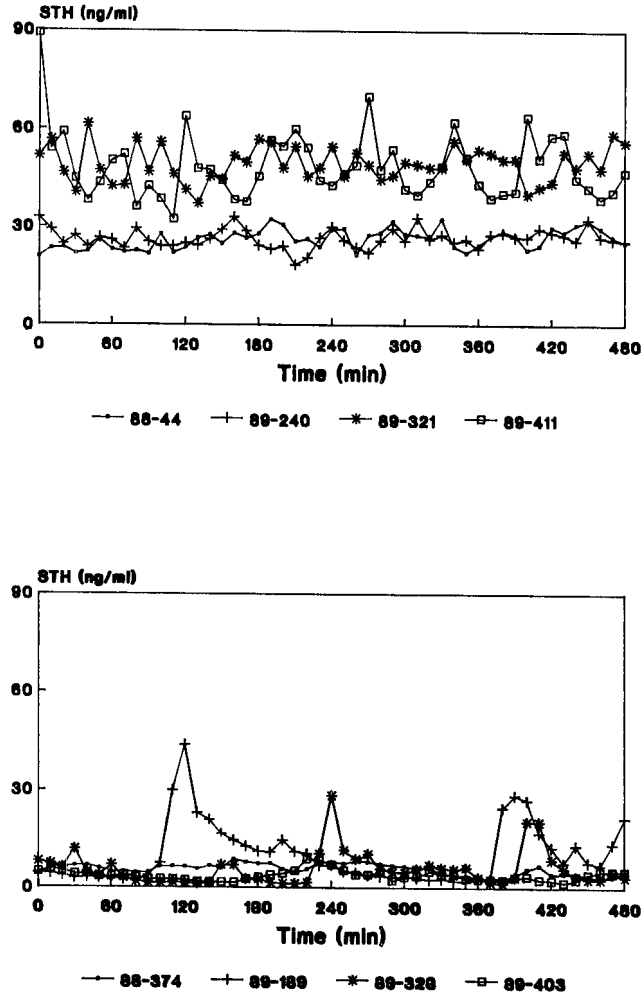

Figure 2. Plasma concentrations of GH in each of eight Brahman calves at 10-min intervals for 8 hr. (Top) Calf 88–44 was a miniature heifer and calves 89–240, 89–321, and 89–411 were miniature bulls. (Bottom) Calf 88–374 was a normal-stature control heifer and calves 89–189, 89–328, and 89–403 were normal-stature control bulls.

Table II. Effect of Calf Type on Circulating Patterns of GH

	Calf type		SE	*P*
	Miniature	Control		
Mean (ng/ml)	37.8	6.2	4.8	0.004
Peaks (no./8 hr)	9.0	4.5	0.7	0.005
Peak amplitude (ng/ml)	37.0	10.1	5.6	0.014

experiments. Data for further analyses were pooled across years and only included data from the miniature type calves (88–44, 89–240, 89–321, and 89–411) and contemporary controls (88–374, 89–189, 89–328, and 89–403).

Effects of calf type on circulating concentrations of IGF-I, T_3, and T_4 are given in Table I. Plasma IGF-I was six times higher in control calves compared with miniature calves ($P = 0.001$). Plasma concentrations of T_3 and T_4 were also higher in control compared with miniature calves ($P = 0.001$), but concentrations of T_3 and T_4 in both calf types were within normal ranges. There were no effects of sampling day ($P > 0.10$), nor were there any interactions between calf type and sampling day for any of these hormones ($P > 0.10$). Feed intake averaged 19.3 ± 10.1 (mean ± SD) g dry matter/kg body wt/day for control calves and 18.6 ± 0.9 for miniature calves, and was not different between calf types ($P > 0.10$).

Plasma concentrations of GH every 10 min for 8 hr are given in Figure 2, and effects of calf type on mean GH, peak frequency (no. peaks/8 hr), and peak amplitude are given in Table II. Mean GH was about six times higher in miniature compared with control calves ($P = 0.004$), and there were twice as many peaks over the 8-hr sampling period in miniature compared with control calves ($P = 0.005$). Relative to mean GH, peak amplitude was low for miniature calves, and was different between calf types ($P = 0.01$), with mean peak amplitude for miniature calves being nearly four times that of controls.

Effects of calf type and plane of nutrition on plasma concentrations of IGF-I and insulin are given in Tables III and IV, respectively. Plasma concentrations of both IGF-I ($P = 0.001$) and insulin ($P < 0.001$) were higher in control compared with miniature calves. Plasma IGF-I tended to decrease with decreasing plane of nutrition and then increase toward initial values upon realimentation (quadratic effect, $P = 0.11$). As with plasma IGF-I, plasma insulin decreased with decreasing plane of nutrition and increased upon realimentation (quadratic effect, $P = 0.006$). There was no calf type × feeding period interaction for either plasma IGF-I or insulin, nor was there any effect of blood-sampling day ($P > 0.10$).

Effect of calf type on plasma glucose response to insulin challenge and plasma insulin concentrations after insulin injections are given in Table V. The hypoglycemic response to insulin injection was greater in miniature compared with control calves at 2 and 6 hr after insulin administration ($P = 0.09$). This exaggerated hypopglycemic response was also evidenced by a trend toward different glucose response curve areas between calf types (−490 vs −656 mg·hr/dl; $P = 0.12$). Plasma insulin concentration was not different at individual sampling times, but the area under the plasma insulin response curve was greater for miniature calves (12.9 vs 29.7 ng·hr/ml; $P = 0.07$).

Results of the clinical chemistry screen are given in Table VI. Several significant differences were observed between calf types. Serum urea nitrogen increased 51% and the urea nitrogen to creatinine ratio increased 40% in miniature calves compared with controls.

Table III. Effects of Calf Type and Plane of Nutrition on Plasma Concentrations of IGF-I (ng/ml)

Calf type	Feeding period			Mean ± SE[c]	P linear effect	P quadratic effect
	1[a]	2[b]	3[a]			
Control	202.7	175.2	186.7	188.2 ± 3.4		
Miniature	47.7	36.1	38.4	40.7 ± 3.4		
Mean ± SE	125.2 ± 4.5	105.7 ± 4.0	112.5 ± 3.6		0.16	0.11

[a] Feeding level, 2.2% of body weight.
[b] Feeding level, 1.1% of body weight.
[c] Significant effect of calf type, $P = 0.001$.

Table IV. Effects of Calf Type and Plane of Nutrition on Plasma Concentrations of Insulin (ng/ml)

Calf type	Feeding period			Mean ± SE[c]	P linear effect	P quadratic effect
	1[a]	2[b]	3[a]			
Control	0.80	0.61	0.79	0.73 ± 0.01		
Miniature	0.39	0.24	0.44	0.36 ± 0.01		
Mean ± SE	0.59 ± 0.01	0.42 ± 0.01	0.62 ± 0.01		0.36	0.006

[a] Feeding level, 2.2% of body weight.
[b] Feeding level, 1.1% of body weight.
[c] Significant effect of calf type, $P < 0.001$.

Table V. Effect of Calf Type on Glucose Response to Insulin Challenge

Time after insulin injection[a]	Plasma insulin (ng/ml)				Plasma glucose (mg/dl)			
	Calf type		SE	P	Calf type		SE	P
	Control	Miniature			Control	Miniature		
0	1.20	0.62	0.35	0.30	103	100	2	0.32
2	2.02	2.51	0.67	0.63	92	60	10	0.09
6	2.47	3.71	0.50	0.15	47	30	5	0.09
12	1.58	1.78	0.26	0.62	72	66	10	0.71
18	1.41	1.01	0.20	0.23	99	97	4	0.74
24	1.50	0.69	0.36	0.18	112	105	3	0.13

[a] Bovine insulin, 0.045 mg/kg$\cdot^{.75}$, im, in 40% (w/v) polyethylene glycol 8000.

Discussion

These data describe an abnormal endocrine condition in miniature Brahman cattle characterized most notably by low plasma concentrations of IGF-I in the presence of high concentrations of plasma GH. This suggests an uncoupling of the normal GH dependence (11) of plasma concentrations of IGF-I. Analysis of circulating patterns of GH in the miniature calves indicated a doubling of peak frequency associated with a 6-fold increase in mean GH, compared with control calves (Table II). Inspection of the GH secretory profile (Fig. 2) revealed relatively high basal GH concentrations in miniature compared with control calves. This high baseline resulted in the average peak amplitude being lower than the mean plasma GH concentrations in the miniature calves. Also, inspection of the GH profiles for miniature calves (Fig. 1) reveals that there may have been more secretory episodes than were recognized by the program used for peak identification and analysis, based on the cut-off criteria established for the measurement of peaks.

The physiological significance of the increased number of plasma GH peaks is not known. However, visual inspection of the secretory profiles of GH in miniature calves suggests that the "pulse generator" for episodic secretion is firing at regular and frequent intervals, apparently unencumbered by normal hypothalamic negative feedback. Normal patterns of GH secretion in cattle do not show the regularity in secretory bursts present in these miniature calves. Normal profiles, as with control calves in this study, suggest a random pattern with fewer episodes and occasional large bursts of secretions (Fig. 2).

Associated with these differences in IGF-I and GH were relatively low circulating concentrations of insulin, T_3 and T_4. A functional relationship between circulat-

Table VI. Effect of Calf Type on a Clinical Screen of Serum Chemistries

Chemistry or ratio	Calf type		SE	*P*
	Control	Miniature		
Glucose (mg/dl)	91	81	3	0.11
Urea nitrogen (mg/dl)	11.3	17.1	0.8	0.02
Creatinine (mg/dl)	1.44	1.58	0.02	0.02
Urea nitrogen to creatinine ratio	7.7	10.8	0.5	0.03
Uric acid (mg/dl)	0.55	0.70	0.04	0.09
Calcium (mg/dl)	10.2	9.2	0.1	0.002
Phosphorus (mg/dl)	7.2	8.9	0.2	0.01
Cholesterol (mg/dl)	119	134	1	0.002
Triglycerides (mg/dl)	23	23	2	0.94
Bilirubin (mg/dl)	0.11	0.11	0.01	0.99
Lactate dehydrogenase (units/liter)	1109	1099	24	0.78
Alkaline phosphatase (units/liter)	362	274	4	0.001
SGOT (units/liter)	56	65	3	0.11
SGPT (units/liter)	14.2	16.3	0.2	0.005
Protein (g/dl)	5.88	5.15	0.06	0.003
Albumin (g/dl)	3.23	2.98	0.02	0.006
Globulin (g/dl)	2.66	2.17	0.03	0.002
Albumin to globulin ratio	1.23	1.41	0.01	0.004
Creatine phosphokinase (units/liter)	133	130	5	0.71
Sodium (m*M*)	137.0	138.8	0.4	0.04
Potassium (m*M*)	4.56	4.61	0.02	0.10
Chloride (m*M*)	103	104	1	0.38
CO_2 (m*M*)	28.3	29.4	0.6	0.31
Anion gap	6.2	5.8	0.6	0.71

ing concentrations of IGF-I and circulating concentrations of thyroid hormones in cattle has been suggested previously (7). A preliminary communication by Hannon and Trenkle (12) reports decreased plasma IGF-I and decreased liver IGF-I mRNA in both induced hypo- and hyperthyroid states in steers. Muscle IGF-I mRNA was increased in steers with an induced hypothyroid state, but was not affected by an induced hyperthyroid state.

Results of the nutritional depletion experiment indicate normal nutritional regulation of circulating levels of IGF-I (7, 10). There was no interaction between calf type and plane of nutrition, with both calf types collectively responding to a decreased plane of nutrition by decreasing circulating levels of IGF-I (Table III). Plasma insulin also responded to plane of nutrition. Ronge and Blum (13) reported similar responses to changes in plane of nutrition for IGF-I and insulin in growing heifers.

Among the other clinical differences observed between miniature and control calves in the present study was a trend toward lower serum concentrations of urea nitrogen in control calves (Table VI). This was likely a result of increased use of nitrogen (amino acids) associated with an increased growth rate in control compared with miniature calves. Average post-weaning growth rate from about 7 to 18 months of age was 0.77 kg/day for control calves and 0.33 kg/day for miniature calves ($P < 0.05$; unpublished). Higher serum calcium in control calves may have been a result of hemoconcentration, as indicated by the concomitantly higher total serum protein in controls (Table VI) (14). Whether this is a true homeostatic difference in blood volume between calf types, or is due to mild dehydration associated with behavioral differences (miniature calves appeared to be more docile) in water consumption, can not be determined from the present data.

Low circulating concentrations of IGF-I (15) in the presence of high concentrations of GH (16, 17) have been noted in an autosomal recessive disorder in humans, Laron dwarfism. This condition in humans is also characterized by hypoglycemia (16, 18), which was evident in the miniature Brahman calves in this study only by a somewhat increased hypoglycemic response to exogenous insulin challenge. Increased plasma insulin concentration following an injection of 0.045 mg bovine insulin/kg body $wt^{.75}$, im, was associated with decreases in plasma glucose that tended to be greater ($P = 0.09$) in miniature than in control calves 2 and 6 hr after insulin injections. At 0 and 24 hr relative to the time of insulin injection, plasma insulin concentration in miniature calves was half that in control calves, but not statistically different due to the small number of calves and the variability observed. Similar differences were shown to be statistically different in another experiment (Table IV). Laron dwarfism is a result of a defect in the human GH receptor (19) and is associated with a lack of circulating GH-binding protein (20–22),

which is known to be the cleaved extracellular domain of the GH receptor (23). Measurement of GH-binding protein in the miniature Brahmans is warranted, but was beyond the scope of the present study.

Dwarfism in cattle is known to exist in several forms (24), the most studied of which, in this country, is the brachycephalic "snorter" dwarf first described by Johnson *et al.* (25). Selection efforts by cattle producers in the United States effectively reduced the gene frequency of the brachycephalic dwarf to the extent that little research on the cause of this disorder continued beyond the early 1960s. Physical aspects of two conditions reported in cattle resemble the miniature Brahman in the present study, namely, the proportionate dwarf Jersey (26) and the midget Brahman (27). No physiological characterization of the proportionate dwarf Jersey was pursued and the line was "discarded" in 1933 (26). Deliberate efforts to breed the midget Brahman ended in 1963 (28) and little research, other than test matings to determine the mode of inheritance of this condition, was accomplished. The midget Brahman was most likely an autosomal recessive and was hypothesized to be the brachycephalic dwarf trait expressed in Brahman cattle (27, 29, 30), but this was never substantiated by repeated matings of midget Brahman and brachycephalic dwarf carrier cattle. An alternative hypothesis would be that the brachycephalic dwarf and the midget Brahman conditions are controlled by allelic genes.

The data presented here describe a miniature condition in Brahman cattle that to our knowledge has not been characterized previously. The condition is manifested by apparently normally proportioned growth, but small stature, and is associated most notably with abnormally low circulating concentrations of IGF-I in the presence of paradoxically high circulating concentrations of GH. This condition appears to be similar to Laron dwarfism in humans, in which the low IGF-I is caused by an abnormality in the GH receptor.

Mention of companies or products is for the benefit of readers and does not constitute an endorsement or preferential treatment by the authors or the USDA. The authors thank Lee Adams, Mary Jane Schoppman, Ed Bowers, Eugene Rooks, Joe Padgett, and the Brooksville Station staff for technical assistance, animal handling, and animal care, and thank Adrian Kozak for assistance with hormone assays. Published as Florida Agricultural Experiment Station Journal Series No. R-01137.

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