MECHANISMS OF ACTION OF ESTROGENS AND ANDROGENS ON PERFORMANCE OF CATTLE - HORMONAL BASIS

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ABSTRACT

Numerous modifications of the endocrine system have been observed in cattle given exogenous anabolic steroids or steroid-like compounds. Changes in concentrations of thyroid hormones, insulin or adrenal corticosteroids probably are not involved directly in the anabolic responses observed with steroid implants. However, extensive evidence indicates that implanted cattle have higher concentrations of plasma growth hormone (GH) resulting from increased secretion (not decreased clearance) of GH from the vascular system. Pituitary glands from implanted steers have a greater number of GH secreting cells. Implanted steers also have a greater number of high-affinity GH receptors in the liver, a greater concentration of mRNA for insulin-like growth factor-1 (IGF-1) in the liver, and increased plasma concentrations of IGF-1 and IGF-1 binding protein-3. All of these changes could result from an increased secretion of GH. However, observations that the growth response and changes in carcass composition of cattle resulting from administration of exogenous GH and steroid implants are additive suggests that the growth responses to these two compounds may be independent; steroids may not act solely through increased secretion of GH. Steroid hormone receptors have been detected in skeletal muscle of cattle and estradiol enhances the concentration of IGF-1 mRNA in bovine muscle. Thereby, steroids and GH may have independent actions on muscle growth.

INTRODUCTION

Somatic growth is the result of interactions between genetics, the environment and supply of nutrients to the body. The endocrine system is the mechanism by which these interactions are coordinated to control growth. Pituitary growth hormone (GH) is essential for somatic growth. The succession starting with regulation of GH secretion in the hypothalamus to release of insulin-like growth factors and their binding proteins by tissues constitutes an elaborate system that is predominant in regulation of growth. This complex is referred to as the somatotrophic axis. Compared with GH, other hormones, such as those from the thyroid, pancreas and adrenal cortex are more permissive than regulatory.

Physiological changes associated with use of anabolic steroids have been studied in numerous cattle experiments to gain some understanding of the growth promoting properties of these compounds. Weights of endocrine glands were measured in the early experiments. Administration of diethylstilbestrol (DES) to steers resulted in increased weights of the anterior pituitary (1,5,24), heavier adrenal glands when DES was implanted (1), but no consistent increase in thyroid weight (5). Following the development of assays to measure hormone concentrations in blood. emphasis was placed on plasma hormones rather than gland weights. Since the initial studies, most of the research dealing with endocrine changes has focused on the somatotrophic axis. Nevertheless, a mode of action of estrogens on growth of cattle has not been definitively established.

Plasma Concentrations of Hormones from the Thyroid, Adrenal and Pancreas

Implanting estrogenic anabolic compounds increases thyroid gland activity, as reflected by increased plasma concentrations of thyroxin (9.14.18). However, estrogen anabolics do not affect plasma concentrations of triiodothyronine. Implanting cattle with trenbolone acetate (TBA) alone or in combination with estradiol decreased thyroxin with no effect on triiodothyronine (9,14,18). In another study with steers, implanting estradiol had no effect on either thyroxin or triiodothyronine (10).

Plasma concentrations of adrenal glucocorticoids of cattle implanted with anabolic steroids have been measured in several experiments. Implanting steers with estradiol tended to decrease corticoids in one study (10) but not another (13). Implanting TBA alone or in combination with estradiol, however, decreased plasma cortisol (13). This decrease in plasma cortisol following implanting with TBA is consistent with the observation of decreased responsiveness of the adrenal cortex to ACTH in TBA-treated sheep (26).

In most studies, plasma insulin is not significantly increased by anabolic implants in cattle (10,19). In situations where there is a trend for plasma insulin to be increased (2,27), the pancreas may be responding to increased feed intake of cattle given anabolic hormones.

Taken together, these experiments do not present convincing evidence that an increase in thyroid hormones and insulin or a decrease in cortisol constitute a primary site of action to explain the effects of anabolic steroids on growth of ruminants. The decrease in cortisol with TBA and the increase in thyroxin with estrogens along with an increase in insulin, however, would contribute to an overall anabolic response.

The Somatotrophic Axis

Heavier pituitary glands which contained more GH relative to body weight (Table 1) was the initial evidence that the somatotrophic axis might be involved in the action of estrogen on growth of ruminants (24). Later, implanting steers with DES was observed to increase DNA content of the pituitary, suggesting that cell number was increased (15). More recently (Table 2), implanting steers with TBA and estradiol was found to increase the number of GH secreting cells in the pituitary (25). These findings indicate that estrogens have some effect either directly on the pituitary or indirectly on the hypothalamus and release of growth hormone releasing hormone (GHRH); this results in pituitaries with an increased capability for secreting GH. One experiment showed that incubation of bovine pituitary cells with estradiol did not significantly increase GHRH-induced GH release, but preincubating the cells with testosterone increased the GH response to a GHRH challenge (12). These results suggest that anabolic steroids may directly affect the anterior pituitary.

Administration of estrogens to cattle by feeding DES or implanting estradiol or zeranol elevates concentrations of GH in plasma (2,4,7,10,11,27). Representative data from one study of steers implanted with estradiol are shown in Table 3. The greater plasma GH concentrations brought about by estrogen implants is not a result of a decrease in clearance of GH from the circulatory system (Table 4), but is due to greater secretion of the hormone (8). Administration of TBA alone to steers does not increase concentrations of GH in plasma (7,13), but steers implanted with TBA plus estradiol (13,19) or TBA plus hexoestrol (7) have greater plasma concentrations of GH than steers without implants.

Table 1. Growth hormone in pituitary glands of steers fed diethylstilbestrol as determined by bioassay[1].

	DES fed, mg/d		
	0	5	10
Anterior pituitary, g	1.18	1.43	1.50
Growth hormone assay			
Width of tibia, μ	269	254	268
Growth hormone index	316	369	405
GH index/100 kg body wt	71.6	78.6	84.6

[1]Struempler and Burroughs (24).

Table 2. Effects of an estradiol implant with trenbolone acetate in steers on growth hormone secreting cells in the pituitary gland[1].

	Cell type			
	Growth hormone	Prolactin	Mammosomatotropin	All growth hormone
Control	10.0	42.0	20.8	30.8
Implant	27.8	40.5	10.7	38.5

[1]Thomson (25).

Growth hormone is secreted during discreet intervals throughout the day. Each period of active secretion is followed by a period of quiescence. Plasma GH profiles of cattle have not been consistently changed by implants (Table 3). Implanting estradiol has been reported to change neither the amplitude nor the frequency of GH peaks (10) and to not increase GH peak height (4). Although implanting steers with TBA and estradiol increased GH peak height in one study (19), implanting had no significant effect (a tendency to decrease) in another study (13). The number of secretory peaks has not been increased by anabolic implants in any of the studies. Bulls which are subjected to increasing concentrations of testosterone during development have greater amplitude of GH peaks during the secretory period (20) as compared with steers or heifers without implants. Administration of estradiol and TBA to steers makes their GH secretion pattern more similar to that of bulls.

The secretion of GH is regulated by a dual system of hypothalamic hormones; GHRH stimulates GH release while somatostatin inhibits GH release. The release of these hypothalamic hormones is influenced by a network of neurotransmitters and extrahypothalamic influences. Steers implanted with estradiol (22) or estradiol and TBA (16) responded with greater secretion of GH in response to venous injection of a combination of GHRH and thyrotropin-releasing hormone or GHRH, respectively. Results of the study with steers implanted with estradiol and TBA are shown in Table 5. These findings are consistent with the concept that administration of estrogens to cattle results in anterior pituitary glands which are more sensitive to release of GH, i.e., their response to GHRH.

Table 3. Effects of an estradiol implant on growth hormone secretory patterns in steers[1].

	GH mean	GH baseline	Peak amplitude	No. peaks
	---------------- ng/ml	----------------		
Control	3.3	2.6	11.9	3.1
Implant	4.6[2]	3.7	9.6	5.2

[1]Grigsby and Trenkle (10)
[2]$P < .05$

Table 4. Effects of estrogen implants in steers on growth hormone secretion and clearance from plasma[1].

	Plasma clearance	Secretion
	------ ml/kg/hr ------	------ μg/kg/hr ------
Control	72.6	.53
DES	63.9	1.04[2]
Zeranol	83.3	1.10[2]
Synovex S	78.0	.96[2]

[1]Gopinath and Kitts (8).
[2]$P < .05$.

Table 5. Effects of an estradiol implant with trenbolone acetate in steers on plasma growth hormone and response to growth hormone releasing hormone[1].

	Growth hormone	GH response to GHRH
	-------- ng/ml --------	---- Area under curve ----
Control	5.7	1894
Implant	8.3	3461

[1]Hongerholt et al. (16).

The conventional tenet is that GH reacts with membrane receptors on liver cells to activate a cascade of intracellular signals to produce insulin-like growth factor-1 (IGF-1), a growth factor for muscle and the skeleton. Estradiol implants markedly increase the number of high capacity GH receptors in bovine liver and marginally increase the number of low capacity GH receptors (4) but have no effect on the dissociation constants of either class of receptors (Table 6). Further down the somatotrophic axis, plasma IGF-1 concentrations in steers (Table 7) implanted with estradiol are elevated (3,11). Adding TBA with estradiol results in even greater plasma IGF-1 in implanted steers (Tables 8 and 9) compared with control steers (17,19). Another indication that anabolic steroids might be acting via the somatotrophic axis is the increase in liver concentration of IGF-1 mRNA (Table 8) in steers either implanted with estradiol, administered exogenous GH, or implanted with estradiol and TBA (11,19). Presumably an increased liver production of IGF-1 might be the anabolic stimulus for greater somatic growth.

Specific proteins present in serum have been found which selectively bind IGF-1 (IGFBP); these play a role in regulation of the biological activity of IGF-1 in tissues. A number of different proteins that bind IGF-1 have been isolated from different tissues and cells. Steers implanted with estradiol and TBA (Table 9) have increased concentrations of IGFBP-3 (17). This binding protein is GH dependent and carries the majority of IGF-1 in plasma. IGF-1 bound to IGFBP-3 presumably is a storage pool of the growth factor in blood. The binding proteins also may play a role in delivery of IGF-1 to cells or control its availability to cells.

Table 6. Effects of an estradiol implant in steers on binding of growth hormone to liver membranes[1].

	Capacity		Dissociation constant	
	--- pmol/100 mg liver ---		-------- pmol/l --------	
	High	Low	High	Low
Control	1.87	20.1	11.6	106.4
Implant	6.56[2]	30.1[2]	10.8	110.6

[1]Breier et al. (4).
[2]$P < .05$.

Table 7. Effects of an estradiol implant in steers on plasma concentrations of growth hormone and insulin-like growth factor-1[1].

	GH	IGF-1	IGF-1[2]
		------------------ ng/ml ------------------	
Control	3.1	60.6	97.5
Implant	4.7[3]	85.2[3]	133.0[3]

[1]Breier et al. (3).
[2]Eight hours after administration of exogenous GH.
[3]$P < .05$.

Table 8. Effects of an estradiol implant with trenbolone acetate in steers on plasma concentrations of growth hormone and insulin-like growth factor-1 and liver concentrations of insulin-like growth factor-1 mRNA[1].

	GH	IGF-1	IGF-1 mRNA
	------------ ng/ml ------------		--- pg/mg ---
Control	1.6	190	10.9
Implant	3.0[2]	264[2]	20.1[2]

[1]Miller (19).
[2]$P < .05$.

Anabolic steroids, especially estradiol, enhance many aspects of the somatotrophic axis in cattle. These steroids may modify either the pituitary or the hypothalamus making the pituitary more responsive to GHRH and thereby causing greater secretion of GH. Subsequent effects on the somatotrophic axis may be the consequence of greater secretion of GH. It is tempting to conclude that this represents the mode of action of estrogen on growth of cattle.

Three experiments have been conducted with cattle to compare the growth responses to anabolic steroids and exogenous GH (6,21,28). All of these experiments show conclusively that the growth responses of cattle to GH and the steroids are additive and probably independent. The results of one study designed to study the independent actions of exogenous GH and estradiol in steers are shown in Figure 1. Based on these results the anabolic response to exogenous steroid hormones by cattle clearly are not due solely to an increase in GH secretion.

Table 9. Effects of an estradiol implant with trenbolone acetate in steers on plasma concentrations of insulin-like growth factor-1 and its binding protein[1].

	IGF-1	IGFBP-3
	------------ % change[2]	------------
Control	0	2
Implant	31[3]	45

[1]Johnson et al. (17).
[2]Change between preimplantation and 40 days post implant.
[3]P < .01.

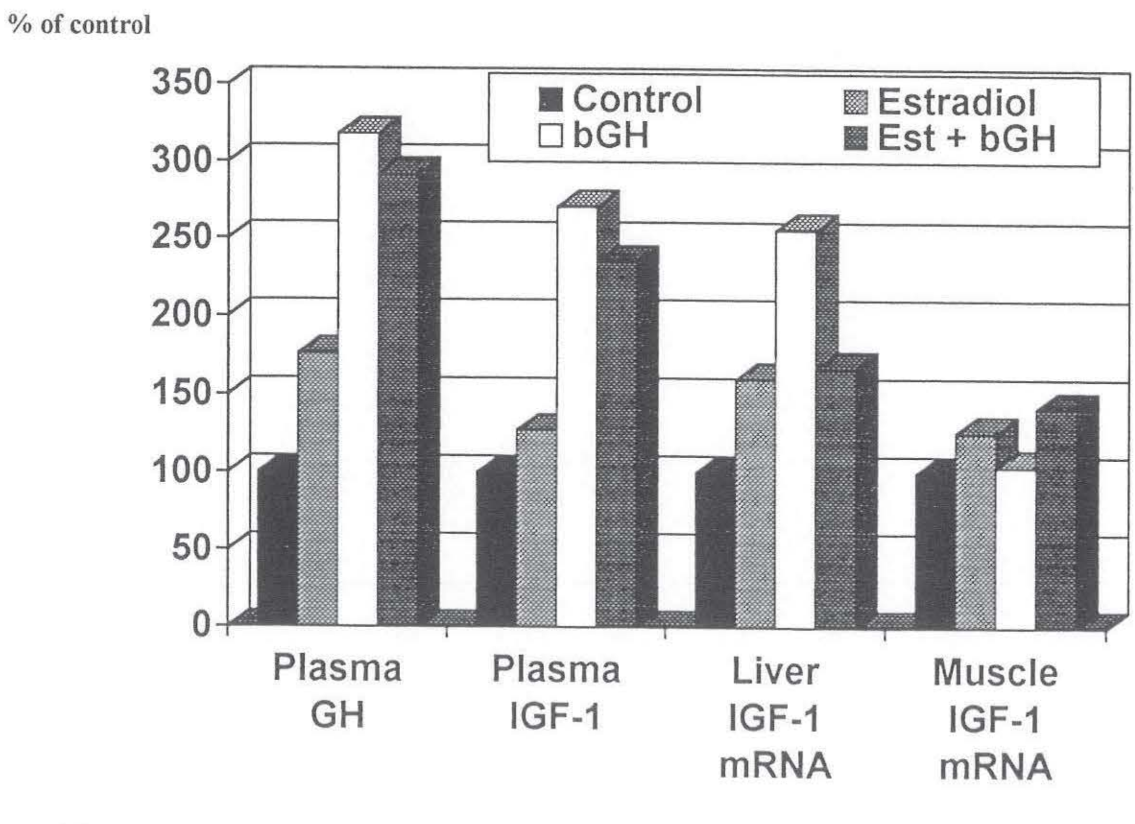

Figure 1.

Receptors for both androgens and estrogens have been found to be present in bovine muscle (23). The concentration of these receptors may increase in physiological states of low steroid concentrations. The presence of these receptors in skeletal muscle opens the possibility that steroid hormones might have some direct effect on growth of skeletal muscle. Implanting steers with estradiol increase IGF-1 mRNA in muscle of steers (Figure 2) to a greater extent than administration of exogenous GH (11) alone. If this is the case, then the growth effects from estradiol must be independent of that from exogenous GH indicating that the principle anabolic response from anabolic steroids is not increased secretion of endogenous GH. The anabolic effects of TBA also may be directly on muscle, but in some manner different from estrogen.

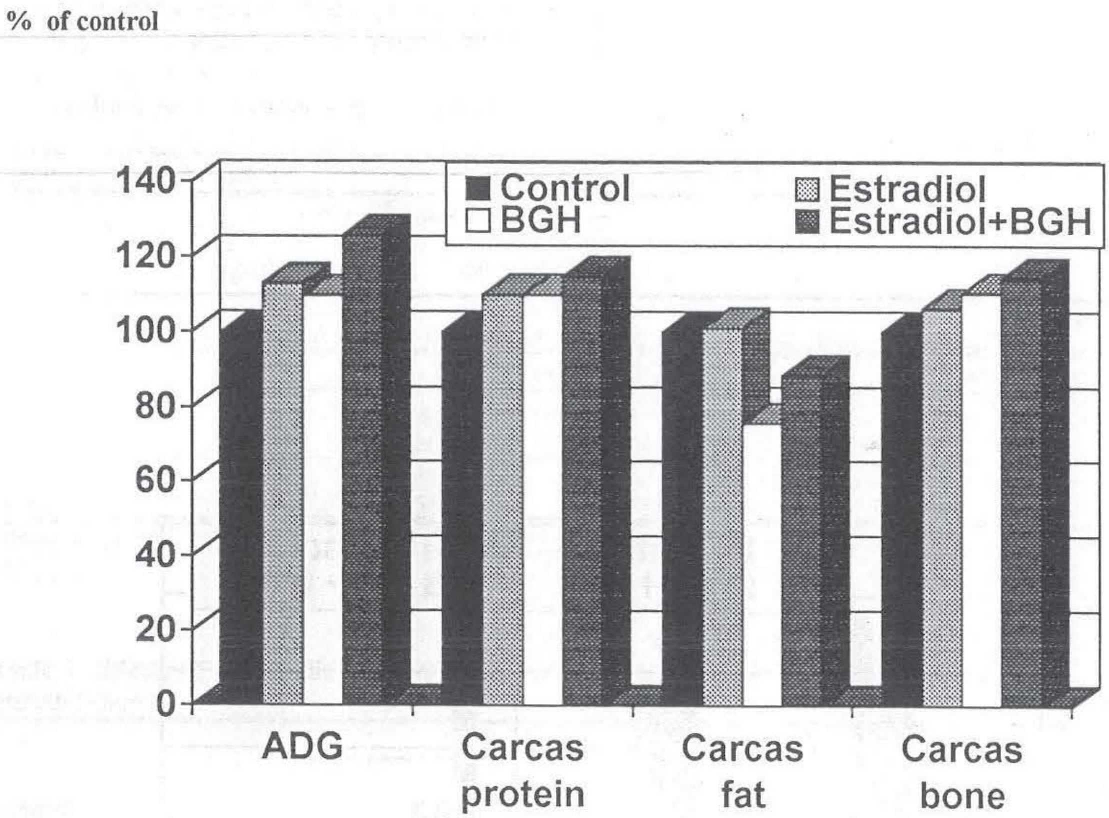

Figure 2.

LITERATURE CITED

1. Clegg, M.T., and H.H. Cole. 1954. The action of stilbestrol on the growth response in ruminants. J. Anim. Sci. 13: 108.
2. Borger, M.L., L.L. Wilson, J.D. Sink, J.H. Ziegler and S.L. Davis. 1973. Zeranol and dietary protein level effects on live performance, carcass merit, certain metabolite levels of steers. J. Anim. Sci. 36:706.
3. Breier, B.H., P.D. Gluckman and J.J. Bass. 1988. Influence of nutritional status and oestradiol- 17-β on plasma growth hormone, insulin-like growth factors-I and -II and the response to exogenous growth hormone in young steers. J. Endocrinology. 118:243.
4. Breier, B.H., P.D. Gluckman and J.J. Bass. 1988. The somatotrophic axis in young steers: influence of nutritional status and oestradiol-17-β on hepatic high-and low-affinity somatotrophic binding sites J. Endocrinology. 118:169.

5. Burgess, T.D., and G.E. Lamming. 1960. The effect of diethylstilbestrol, hexoestrol and testosterone on the growth rate and carcass aquality of fattening beef steers. Anim. Prod. 2: 93.
6. Enright, W.J., J.F. Quirke, P.D. Gluckman,, B.H. Greier, L.G. Kennedy, I.C. Hart, J.R. Roche, A. Coert and P. Allen. 1990. Effects of long-term administration of pituitary-derived bovine growth hormone and estradiol on growth of steers. J. Anim. Sci. 68:2345.
7. Galbraith, H. and H.B. Watson. 1978. Performance, blood and carcass characteristics of finishing steers treated with trenbolone acetate and hexoestrol. Vet. Record 103:28.
8. Gopinath, R., and W.D. Kitts. 1984. Growth hormone secretion and clearance rates in growing beef steers implanted with estrogenic anabolic compounds. Growth 48: 499.
9. Gopinath, R., and W.D. Kitts. 1984. Plasma thyroid hormone concentrations in growing beef steers implanted with estrogenic anabolic growth promotants. Growth 48: 515.
10. Grigsby, M.E. and A. Trenkle. 1986. Plasma growth hormone, insulin, glucocorticoids and thyroid hormone in large, medium and small breeds of steers with and without an estradiol implant. Dom. Anim. Endocrinology 3: 261.
11. Hannon, K.M. 1990. Hormonal regulation of bovine liver and skeletal muscle IGF-1 mRNA. PH.D. Dissertation, Iowa State University.
12. Hassan, H.A., R.A. Merkel, W.J. Enright and H.A. Tucker. 1992. Androgen modulate growth hormone-releasing factor-induced GH release from bovine anterior pituitary cells in static culture. Dom. Anim. Endocrinology. 9:209.
13. Hayden, J.M., W.G. Bergen and R.A. Merkel. 1992. Skeletal muscle protein metabolism and serum growth hormone, insulin, and cortisol concentrations in growing steers implanted with estradiol-17β, trenbolone acetate, or estradiol-17β plus trenbolone acetate. J. Anim. Sci. 70:2109.
14. Heitzman, R.J., I.A. Donaldson and I.C. Hart. 1980. Effect of anabolic steroids on plasma thyroid hormones in steers and heifers. Brit. Vet. J. 136:168.
15. Hinds, F.C., T.C. Detwiler, H.H. Draper, G.E. Mitchell, Jr. and A.L. Neumann. The influence of estradiol-progesterone and DES implants on the RNA and DNA content of anterior pituitaries from fattening steers. J. Anim. Sci. 18:1568. (Abst)
16. Hongerholt, D.D., B.A. Crooker, J.E. Wheaton, K.M. Carlson and D.M. Jorgenson. 1992. Effects of a growth hormone-releasing factor analogue and an estradiol-trenbolone acetate implant on somatotropin, insulin-like growth factor I, and metabolite profiles in growing Hereford steers. J. Anim. Sci. 70:1439.
17. Johnson, B.J., M.R. Hathaway, P.T. Anderson, J.C. Meiske and W.R. Dayton. 1996. Stimulation of circulating insulin-like growth factor I (IGF-1) and insulin-like growth factor binding proteins (IGFBP) due to administration of a combined trenbolone acetate and estradiol implant in feedlot cattle. J. Anim. Sci. 74:372.
18. Kahl, S., J. Bitman and T.S. Rumsey. 1978. Effect of Synovex-S on growth rate and plasma thyroid hormone concentrations in beef cattle. J. Anim. Sci. 46: 232.
19. Miller, K. 1996. Relationship of implantation (estradiol 17-β and trenbolone acetate) and dietary protein source on the growth rates, carcass characteristics, and hormonal profiles of growth hormone, insulin and insulin-like growth factor-1 in cattle. M.S. Thesis. Iowa State University Library.
20. Plouzek, C.A. and A. Trenkle. 1991. Growth hormone parameters at four ages in intact and castrated male and female cattle. Dom. Anim. Endocrinology. 8:63.
21. Preston, R.L., S.J. Bartle, T.R. Kasser, J.W. Day, J.J. Veenhuizen, and C.A. Baile. 1995. Comparative effectiveness of somatotropin and anabolic steroids in feedlot steers. J. Anim. Sci. 73:1038.
22. Rumsey, T.S., T.H. Elsasser and S. Kahl. 1996. Roasted soybeans and an estrogenic growth promoter affect growth hormone status and performance of beef steers. J. Nutr. 126:2880.
23. Sauerwein, H., and H.H.D. Meyer. 1989. Androgen and estrogen receptors in bovine skeletal muscle: relation to steroid-induced allometric muscle growth. J. Anim. Sci. 67:206.
24. Struempler, A.W., and W. Burroughs. 1959. Stilbestrol feeding and growth hormone stimulation in immature ruminants. J. Anim. Sci. 18: 427.
25. Thomson, D.U. 1996. In vitro muscle cell protein synthesis and degradation, nitrogen balance and the feedlot response to trenbolone acetate, estradiol, and somatotropin in finishing beef steers. PH.D. Dissertation. Texas Tech University.

26. Thomas, K.M. and R.G. Rodway.1982. Supression of adrenocortical function in rats and sheep treated with the anabolic steroid trenbolone acetate. Proc. Nutr. Soc. 41: 138A.
27. Trenkle, A. 1970. Plasma levels of growth hormone, insulin, and plasma protein-bound iodine in finishing cattle. J. Anim. Sci. 31: 389.
28. Wagner, J.F., T. Cain, D.B. Anderson, P. Johnson and D. Mowrey. 1988. Effect of growth hormone (GH) and estradiol (E2β) alone and in combination on beef steer growth performance, carcass and plasma constituents. J. Anim. Sci. 66:283. (abst).

QUESTIONS & ANSWERS

Q: How might the decrease in cortisol seen with implants alter the decision to implant or not implant stressed calves?

A: At one time, Ralgro implants were reputed to decrease shrink of transported calves and it was being promoted for such use. I haven't heard anything about that recently. Implanting might reduce shrink and thereby prove beneficial.