Introduction

The livestock industries utilize numerous means to alter the performance of meat animals and composition of their resulting carcasses. Inclusion of metabolic modifiers in production systems reflects a continuation of processes that began decades ago with genetic selection and progress in understanding of nutrition, health, and management.

Any drug or management practice that affects efficiency of food animal production exerts its influence through at least one of three general mechanisms:

- increased energy consumption above maintenance,
- altered composition through reduced energy content of the empty body, or
- improved efficiency of the processes that result in growth.

This paper will focus on the effects of metabolic modifiers currently being used in the livestock industry, the mechanisms by which they exert their effects, and discussion of some practical considerations for their use. The primary example will be steroid growth implants in beef cattle. Other modifiers will be discussed as their effects differ from steroids.

Steroid Growth Implants

In the U.S., virtually all confined, fed cattle receive steroid growth implants as do a large portion of non-confined (pasted) cattle. Producers use implants to receive the economic benefit of increased average daily gain (ADG) and improved feed conversion efficiency (F/G). These performance enhancements typically improve profitability by $20-40 per head (Anderson, 2000). The beef industry benefits from implant use due to reduced cost of production (Gill and Trapp, 1997), the authors contend that reduced costs result in significantly greater market share for beef. These benefits could be diminished if consumer acceptance of beef products from implanted cattle is reduced.

Steroid implants for beef cattle include estrogens and androgens. Steroids are manufactured as compressed pellets containing a high proportion of drug and some inert carrier (Compudose® and Encore® are estradiol-impregnated silastic implants; all other products are compressed pellets). Implant products are administered subcutaneously in the middle one-third of the ear and release drug over an extended period of time. Steroids are transported in the blood bound to various proteins, with only 1-3% available as free steroid. Many steroids undergo conversion to other steroid molecules, either in the blood or within various cell types. The most significant of these conversions is the aromatization of testosterone to estradiol, much of which occurs in skeletal muscle and is responsible for a portion of testosterone effects. For review of steroid carrier proteins and steroid interconversions, see Hancock et al. (1991).

Once in the blood, steroids exert their influence on growth through the classic steroid mode of action. The hormone:receptor complex is internalized which ultimately results in disruption of the shape of DNA allowing binding of transcription factors to exposed sequences. The net effect is translation of both early- and late-cascading protein sequences.

Estrogens

Estrogenic implants contain either the naturally occurring steroid, estradiol, in one of three forms, or the synthetic estrogen, zeranol. Steroid molecules with estrogenic activity are nearly ubiquitous in animal and plant life but despite this (or perhaps because of it) we have only a simplistic understanding of how they exert their effects on food-producing animals.

Estrogenic implants have been shown to increase feed consumption in most typical feeding studies (Anderson and Botts, 1995). With average daily feed intake (ADFI) increased by approximately 6% in steers, energy available for growth increases by approximately 10% (maintenance requirements are also increased slightly with estrogen administration).

While increases in ADFI are correlated with increases in mean live weight, this is not a causal relationship (Anderson and Botts, 1995). Increased ADFI is observed within the first
few days of estrogen administration and thus increases before meaningful changes in live weight are observed. Increased feed consumption is likely brain mediated but little detail has been provided by research in cattle. ADFI is increased in dose-dependent fashion, up to practical limits of estrogen administration.

Increased ADFI does not explain all of the ADG increase in response to estrogen administration in cattle (Table 1); altered composition likely accounts for the remainder. Effects of estradiol on carcass composition are primarily a result of indirect mechanisms. Although bovine muscle has estradiol-binding capability (Meyer and Rapp, 1985; Sauerwein and Meyer, 1989), it is not clear that significant growth effects result from intracellular effects of estradiol binding. It is likely that the greater effects of estradiol are mediated through alteration of the somatotrophic axis. Estradiol administration increases pituitary size and the proportion of somatotrophs as well as increasing the sensitivity of the pituitary to somatotropin releasing hormone. These effects result in increased circulating somatotropin (Gopinath and Kitts, 1984; Grigsby and Trenkle, 1986; Breier et al., 1988a) in response to estradiol treatment. The effects of somatotropin and the ability of the animal to respond become greater as well. Somatotropin receptors and hepatic somatotropin binding ability are increased (Breier et al., 1988b), primarily in high capacity receptors. In other work, production of somatotropin-induced growth factors has been increased by estradiol administration (Hongerholt et al., 1992). Other metabolic hormones such as insulin and the thyroid hormones have lesser roles in mediating estrogen actions (Grigsby and Trenkle, 1986).

Although estradiol activity is mediated through the somatotrophic axis, estradiol and somatotropin show additive, independent effects (Enright et al., 1990; Preston et al., 1995). Thus, it appears that the mechanism of estradiol activity is not limited to increased somatotropin secretion or efficacy. Evidence for this is available in the results of protein metabolism experiments. Somatotropin enhances protein accretion by increasing protein synthesis, without affecting the rate of protein degradation (Bergen, 1974; Goldberg et al., 1980; Buttery, 1983), whereas estradiol effects appear to be a result of diminished protein degradation (Buttery, 1983; Sinnett-Smith et al., 1983). In fact, Tucker and Merkel (1987) suggested that both synthesis and degradation (to a greater extent) are reduced with estrogen administration.

### Androgens

The naturally occurring androgen, testosterone, is included in some implant products approved for heifers, but is not approved for use in steers. Trenbolone, a synthetic androgen is approved for use in steers and heifers, in the form of trenbolone acetate (TBA). TBA is readily de-acetylated in the blood stream. Several products are available which contain both TBA and estradiol; this TBA+E combination is typically the most effective growth promotion strategy. Neither testosterone, in commercially feasible doses, or TBA, administered without estradiol, is particularly effective in steers (Anderson, 1991). TBA is highly effective in heifers, or in steers, when co-administered with estradiol. TBA is preferable to testosterone because it is more anabolic and less androgenic (Anderson, 1991).

In contrast to estradiol, androgens have direct effects on muscle cells that contribute significantly to their activity. Muscle cells have ability to bind androgens (Sinnett-Smith, et al., 1987; Sauerwein and Meyer, 1989). While testosterone increases both protein synthesis and degradation rates in skeletal muscle, TBA reduces both rates (Tucker and Merkel, 1987). In either case, protein accretion can be increased but the TBA-induced mechanism is favorable because it is less energy expensive to the animal.

The indirect effects of androgens are significant as well. Foremost among these is interference in the effects of corticosteroids. Androgens interfere with the anti-anabolic effects of the corticosteroids in several ways. TBA implantation diminishes circulating cortisol (Hayden et al., 1992), in part by reducing responsiveness to ACTH (Thomas and Rodway, 1983). In addition, androgens compete for corticosteroid binding sites (Mayer and Rosen, 1975; Sauerwein and Meyer, 1989) and down-regulate corticosteroid receptors.

As with estradiol, other metabolic hormones are altered in response to androgen administration. However, the net effect of these changes is minor relative to other mechanisms (Trenkle, 1997).

### TABLE 1. Responses to steroid growth promotants in feedlot cattle, compared to negative control.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Comparisons</th>
<th>ADG, %</th>
<th>F/G, %</th>
<th>Choice+Prime %</th>
<th>HCW, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steers</td>
<td>Estrogen-containing implant programs</td>
<td>226</td>
<td>15.0</td>
<td>7.2</td>
<td>-8.0</td>
</tr>
<tr>
<td>Heifers</td>
<td></td>
<td>53</td>
<td>6.5</td>
<td>3.6</td>
<td>-8.7</td>
</tr>
<tr>
<td>Steers</td>
<td>Implant programs containing estrogen and trenbolone acetate</td>
<td>337</td>
<td>20.9</td>
<td>11.2</td>
<td>-15.2</td>
</tr>
<tr>
<td>Heifers</td>
<td></td>
<td>61</td>
<td>15.7</td>
<td>10.5</td>
<td>-4.9</td>
</tr>
</tbody>
</table>

VetLife Implant Research Database, 2000
Androgen:Estrogen Combinations

The combination of TBA-E appears to produce many of the growth-enhancing effects of the separate drugs and evidence exists that both estrogenic and androgenic mechanisms are involved. In both steers and heifers, the TBA-E combination produces greater growth responses than either drug, used alone (Table 1). Indeed, these products represent the most potent metabolic modifiers currently available to the U.S. cattle industry.

Of practical significance, most TBA-E treatments reduce marbling of feedlot cattle, resulting in a lower percentage of cattle that qualify for the preferred quality grades, Choice and Prime. In studies where marbling scores were low in non-implanted cattle, the proportion of carcasses with marbling scores low enough to be placed in the heavily penalized quality grades was often increased by implanting with TBA-E. The difference in marbling between control and TBA-E-implanted cattle is diminished if the implanted cattle are harvested at much heavier weights than controls (Anderson et al., 1991).

The time course of responses to TBA-E is of particular interest. TBA-E administration results in rapid, hypertrophic effects. In many studies in which interval performance data were reported, TBA-E increased ADG by 50-60% during the first 30-60 days of the experiment (Anderson, 2000). In the work of Thomson (1996), ADG was nearly doubled in steers that were harvested 21 days after their first exposure to TBA-E. The rapid weight gain is largely due to stimulation of muscle growth. Johnson et al. (1996a) reported that carcass protein deposition was increased by 82% during the first 40 days after TBA-E administration. This early muscle growth appears to be entirely due to hypertrophy (Sinnett-Smith et al., 1983) as muscle RNA and DNA concentrations are diminished.

The possibility of hyperplasia in response to TBA-E exists as well. Johnson et al. (1996a) observed increased ADG in steers treated with TBA-E. These steers also showed elevated serum IGF-I and increased IGFBP-3. Both effects were significant at 21 days post-implantation (the earliest sampling period) and diminished near the end of the feeding period. Johnson et al. (1996a) have shown that chronic administration of TBA-E can result in localized increases in IGF-I mRNA in liver (wethers) and longissimus muscle (steers). These researchers had previously shown that serum from TBA-E-treated steers had increased mitogenic capability in cultured muscle cells (Johnson et al., 1996b) and showed that satellite cells of treated steers were activated in response to TBA-E (Johnson et al., 1998b) resulting in higher maximum fusion percentage and a greater number of myotube nuclei. Taken together, these results allow the possibility that muscle growth responses to TBA-E which appear shortly after administration are due simply to hypertrophy of the muscle cell but that chronic exposure to the drugs allows satellite cell proliferation, resulting in hyperplasia later in the feeding period.

Research and field data have shown that the incidence of dark cutting carcasses (DC) can be increased with TBA+E use. Presence of exogenous steroids can result in sexual or aggressive behavior in feedlot cattle. These effects can cause or increase agonistic behavior, which could cause depleted glycogen stores and ultimately a higher incidence of DC within a pen. This is particularly likely if pens of cattle are mixed prior to transport or slaughter. Direct effects on muscle metabolism may also be involved as calories are diverted toward protein deposition. This would make glycogen depletion more likely under stressful circumstances when TBA+E is used. Additionally, TBA+E could hinder replenment of glycogen reserves, making the animal susceptible to DC even a few days after stress.

Sex steroids have no direct effects on adipose tissue. In many cases, carcass fatness, expressed as a percentage of weight, was not altered in time-constant comparisons of steroid-treated cattle to negative controls. When compared at similar weight endpoints, treated cattle are much leaner. Johnson et al. (1996a) demonstrated that leaner carcasses in TBA+E-treated steers were due to a greater rate of carcass protein deposition, whereas the rate of carcass fat deposition was unaltered. This is similar to differences between bulls and steers (Anderson et al., 1988).

Phenethanolamines

The phenethanolamine ractopamine, a selective β2 agonist has recently been approved for use in the U.S. As of this writing, ractopamine has not been marketed but it is anticipated that inclusion of ractopamine in swine diets, for the purpose of improving feed conversion and carcass leanness, will begin soon. Zilpaterol, a β1 agonist, is approved for use in cattle in Mexico and South Africa.

Excellent reviews of phenethanolamine efficacy and mechanism of action are available (Anderson et al., 1991; Mersmann, 1998). This paper will briefly summarize their effects and mechanisms and comment on some practical considerations of phenethanolamine use.

Phenethanolamine administration results in large improvements in live animal performance and carcass leanness in cattle, sheep or swine (Table 2) with some differences depending on the drug and dosage chosen. Feed consumption is typically depressed slightly in response to phenethanolamines. The net effect is approximately 20% more lean muscle mass per unit of energy input.

Through direct cAMP-mediated effects on adipose tissue, phenethanolamines increase lipolysis and decrease lipogenesis. Further reduction in fatness is effected through nutrient partitioning, as protein deposition is favored.

In muscle, phenethanolamine administration results in increased protein deposition and greater lean mass. This is a result of muscle hypertrophy and changes toward larger muscle fiber types. These effects are thought to be a direct result of activation of β receptors but this has not been conclusively proven in livestock species. Ractopamine, a β1 agonist increases protein synthesis but does not affect protein degradation (Bergen et al., 1989) whereas β2 agonists have anabolic effects on both processes (Moloney et al., 1991). Ractopamine has been further shown to increase abundance of skeletal muscle specific mRNA in vivo and in vitro (Bergen et al., 1989; Helferich et al., 1990).
Livestock production systems may need to be redesigned in order to receive maximum benefit from phenethanolamine use. Because lean tissue deposition is increased without a corresponding increase in feed consumption, nutrient density of the diet must be increased. It is clear that phenethanolamine-treated animals of several species respond to increased dietary protein and there is some evidence that a portion must be ruminal escape protein in cattle or sheep. Other nutrients have not been studied. The effects of phenethanolamines are sufficiently great that their use may require a complete re-work of nutrient requirements.

Phenethanolamines have been shown to be effective in both high and low genetic merit lines of animals but the ideal types of animals for their use have not been identified. In light of occasional negative palatability results with phenethanolamines, use of cattle with high genetic capability to deposit marbling may be important for success with these compounds. This could even be true with some lines of swine. In either case, selection and management for tenderness instead of marbling would be preferred. Research with TBA+E has shown that marbling reductions can be minimized with proper management, but the industry learned some of these management practices the hard way. On the other hand, if marketing systems that allow for beef to be priced on lean weight alone are developed, phenethanolamine benefits will be substantial.

To apply phenethanolamines to commercial swine or cattle feeding operations will require precise management. Feed manufacturing and delivery must be adequate to provide all animals with the proper amount of these potent drugs, which will have very low inclusion rates. In addition, because phenethanolamines are often effective for a limited time period due to desensitization of receptors, and because withdrawal of the drug for an extended period of time could result in substantial lessening of benefits, precise estimates of harvest time for animals must be made at the time of treatment onset. In the current cattle business this is not possible for most feeders.

**Somatotropins**

Use of exogenous somatotropins to influence growth or composition of food animals has not been approved in the U.S. but approval is being sought. Endogenous somatotropins are a primary regulator of growth and composition, directly and through influence on metabolic hormones such as the insulin-like growth factors, insulin and others. Altered production and release of endogenous somatotropins is a primary means through which other metabolic modifiers induce their effects. Nonetheless, somatotropin effects can be additive or complementary to other modifiers such as estrogen (see above).

The effects of exogenous somatotropin can be striking (Etherton and Bauman, 1998, Table 3). Reported effects on ruminants are less dramatic than those observed in swine but this may be a result of experimental diets which are not properly designed to meet the needs of treated animals. When amino acid supply to the gut is increased, somatotropin effects are greater (Boyd et al., 1991; Houseknecht et al., 1992). It is common for efficiency, but not gain, to be improved in cattle treated with somatotropin. In some ruminant studies, the majority of stimulated weight gain is in non-carcass tissues.

Mechanism of exogenous somatotropin action has been summarized (NRC, 1994; Etherton and Bauman, 1998). Synthesis of skeletal muscle protein is increased with little effect on protein degradation, resulting in increased protein accumulation. In adipose, lipogenesis is decreased and lipolysis is increased. These results are dependent on energy balance of the animals in the study.

It is not clear that administration of exogenous somatotropin will be the most appropriate means to manipulate the somatotropic axis in beef cattle or swine. Perhaps administration of releasing factors, which stimulate endogenous somatotropin, or inhibition of somatostatin through some means, may make more sense either due to greater efficacy or practicality of delivery. Research published to date does not provide compelling support for use of exogenous somatotropin in beef cattle.

**Summary**

Compounds with the ability to modify growth and carcass composition of food-producing animals are a significant part of the current food production system. Of all such compounds, steroid growth implants for cattle have had the greatest economic impact over the past few decades. Implants and other modifiers improve the competitive position of the meat industries in which they are used. The primary benefits to the producer are lowered cost of production and increased output per unit of production capacity. Post-harvest, processors and consumers can benefit from lowered costs as well as in-

### TABLE 2. Typical responses to phenethanolamine administration in food producing animals.

<table>
<thead>
<tr>
<th></th>
<th>Ruminants</th>
<th>Swine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average daily gain</td>
<td>+ 10-30%</td>
<td>+ 0-10%</td>
</tr>
<tr>
<td>Feed conversion efficiency</td>
<td>+ 15-30%</td>
<td>+ 5-15%</td>
</tr>
<tr>
<td>Carcass fatness</td>
<td>- 5-30%</td>
<td>-10-15%</td>
</tr>
</tbody>
</table>

**TABLE 3.** Typical responses to exogenous somatotropin administration in swine.

<table>
<thead>
<tr>
<th></th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average daily gain</td>
<td>+ 10-20%</td>
</tr>
<tr>
<td>Feed conversion efficiency</td>
<td>+ 13-33%</td>
</tr>
<tr>
<td>Carcass fat deposition</td>
<td>- 70%</td>
</tr>
<tr>
<td>Carcass protein deposition</td>
<td>+ 62%</td>
</tr>
</tbody>
</table>
increased leanness or other changes in end product characteristics. The introduction of phenethanolamines, initially used in swine, will result in significant industry changes and need for considerable application research, both pre- and post-harvest. Use of new and existing metabolic modifiers must be continually reevaluated, considering production benefits and consumer preferences.

References


