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Pharmaceuticals, direct-fed microbials, and enzymes for enhancing growth and feed efficiency of beef

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Reducing the cost of beef production necessitates improving the ratio of outputs to inputs. This need can be addressed at the operation level by altering the management system or at the individual animal level by altering inherent biologic productivity and efficiency. Numerous products have been developed throughout the years to reduce production costs by improving animal growth rate and the efficiency with which feed is used. Using currently available performance-enhancing products, rate and efficiency of growth typically are improved from 5% to 20% and 3% to 10%, respectively.

The objective of this article is to provide a brief review of the types of products commonly used in one or more countries of North America to enhance performance of growing beef cattle. Aspects most directly related to rate and efficiency of growth and end-product characteristics are addressed. Other considerations (eg, potential effects on animal health, regulatory limitations of use in specific countries, and so forth), although important, are beyond the scope of this article.

Anabolic implants

Currently, there are at least 40 subcutaneous anabolic implants approved for use in one or more countries in North America. Of these, approximately half are generic bioequivalents. Formulations include estradiol 17β (E_2) and its esterified form, estradiol benzoate (E_2B; 72% E_2), zeranol, trenbolone acetate (TBA), testosterone propionate, and progesterone. Readers can find several reviews on this subject published in recent years [1–3].

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Implant structure and function

Implants vary in anabolic compound (type and dose), excipient (carrier) material, and release characteristics. Most implants are of conventional structure, consisting of 2 to 10 identical compressed, cylindric pellets. Principal excipients are cholesterol, lactose, and polyethylene glycol. Pellets gradually dissolve during exposure to body fluids, releasing anabolic compounds into circulation. Release rate and duration (payout) are functions primarily of concentration of anabolic compound, excipient solubility, and pellet hardness. Lactose- and cholesterol-based implants generally have been considered relatively short- and long-acting, respectively, because of their different solubilities; however, performance results are not completely consistent in this regard [4]. An alternative structure consists of an inert silicone core covered by a thin layer of silicone impregnated with micronized crystals of E_2. Antibiotic has been added to some implants to reduce the risk of infection at the site of implantation. Additions have been in the form of a powder coating the external surface of the implant or as an additional pellet that dissolves within a few days of administration.

Wagner [5] reported that the E_2 release pattern from a silicone implant consisted of an initial "burst" followed by a prolonged decline such that slightly more E_2 was released during the first 28 days than was released during the following 112 days (approximately 5.2 versus 4.7 mg). Conventional compressed pellet implants follow a similar pattern. Because clearance of anabolic compounds by the liver and kidney is rapid (eg, E_2 half-life is <1 hour), circulating concentrations primarily reflect release characteristics from the implant [5]. Administration of E_2 in the same implant with TBA prolongs elevated E_2 serum concentrations, suggesting a physical interaction [6]. Testosterone and progesterone seem to interact similarly with E_2 [7].

Physiologic and metabolic effects

Growth-promoting implants supply E_2 either in free form, identical to that of endogenous origin, or as E_2B, which is hydrolyzed rapidly to the free form. The steroidal hormone is lipophilic and passes easily through cell membranes by facilitated diffusion [6]. E_2 binds to estrogen receptors in the cell cytosol, and the hormone-receptor complex migrates into the nucleus, binds to DNA, and either activates or inactivates specific genes [8,9].

Estimates of dose of E_2 necessary to elicit a maximum growth response have been inconsistent. Wagner [5] reported maximum growth response in finishing steers with 54 μg E_2/d; however, Preston and Herschler [10] suggested it may be at least 174 μg/d.

Anabolic mechanisms have been reviewed recently [2,3,11]. Pituitary size and cell numbers are increased by E_2, as is pituitary sensitivity to hypothalamic growth hormone–releasing hormone. Secretion and plasma concentrations of growth hormone (GH) are increased. Elevated plasma

GH and GH receptor numbers in the liver stimulate synthesis and secretion of insulin-like growth factor 1 (IGF-1). IGF-1 mediates GH effects in target tissues; however, exogenous GH and E_2 are additive, indicating that GH cannot be the sole mechanism mediating E_2 effects. Estrogen receptors are present in muscle, and E_2 increases IGF-1 mRNA in muscle cells. E_2 has no effect or causes a slight increase in concentrations of thyroid hormone and cortisol in blood as well as metabolic rate. Plasma urea nitrogen declines within a few days of E_2 administration, reflecting lower catabolism and greater retention of amino acids. E_2 increases protein accretion, probably as a result of increased rate of protein synthesis [12], with either no change or a smaller increase in physiologic degradation.

Zeranol is an anabolic compound belonging to a class of chemicals known collectively as *resorcylic acid lactones*. It is derived by minor modification (ketone reduction) of zearalenone, a compound originally isolated from corn infected with the fungus *Gibberella zeae*. Maximum growth response in finishing steers is achieved with approximately 700 μg/d [13,14]. Zeranol binds to estrogen receptors, although probably with less affinity than E_2 [15]. However, zeranol's physiologic effects are qualitatively those of E_2.

TBA is a synthetic androgenic steroid. It has 8 to 10 times the anabolic potency of testosterone but is only 3 to 5 times as androgenic [16]. On release from the implant, TBA is hydrolyzed rapidly to its active form, trenbolone 17β. Serum concentrations of approximately 100 pg/mL have been associated with increased growth rates in steers that received a commercial implant containing 140 mg of TBA [17]. Higher concentrations (>300 pg/mL) have not always been more effective [12]. Trenbolone 17β binds to androgen and glucocorticoid receptors. Increased protein accretion due to reduced degradation has been reported [18] and would be consistent with the blocking of cortisol's catabolic effects by trenbolone 17β binding to glucocorticoid receptors. It also would be complementary to the effects of estrogens and could provide an explanation for the synergistic effects of androgens and estrogens on performance. Metabolic rate is reduced by doses of at least 0.8 mg/kg body weight [19].

The anabolic effect of testosterone is well documented [20]; however, the dose of 200 mg of testosterone propionate (equivalent to 167 mg of testosterone) included in available commercial implants, with a payout of approximately 100 days (1.7 mg/d or less), is far below the 8 mg/d that Faulkner et al [21] found to be ineffective in heifers. Testosterone propionate's contribution to implant efficacy is more likely through a physical interaction with E_2B that prolongs release and circulating concentration of E_2, as mentioned previously.

Several studies indicate no direct effect of progesterone on growth [22–24]. As with testosterone propionate, progesterone's contribution to improved performance seems to be one of prolonging release and sustaining blood E_2 concentration.

Impact on performance

Extensive reviews of implant effects on cattle performance have been published and should be referred to for a detailed discussion of this topic [25–27]. They cover hundreds of trials conducted in a wide range of production conditions. Typical weight gain response of suckling calves was 4% to 8%. In grazing cattle, responses were reported to be somewhat greater (8%–18%). Across a large number of implanting strategies, intake, weight gain, and efficiency of feedlot cattle were improved 7% to 12%, 8% to 34%, and 2% to 20%, respectively. Several factors can affect the magnitude of the response.

Implant potency refers to anabolic stimulus and is a function of the compounds used, dose relative to animal size, and the time over which it is released. Potency increases with dose up to a maximum, beyond which no further growth is elicited, and negative side effects become more likely. The potency of estrogenic and androgenic compounds in combination (ie, E_2 plus TBA and zeranol plus TBA) is greater than either alone because of complementary mechanisms by which they affect growth. Classification of implants according to potency generally has been based on a combination of differences in dose, payout, and field trial results [28]. Two implant formulations currently available are considered low potency (36 mg of zeranol and 10 mg of E_2B plus 100 mg progesterone). They are most appropriate for suckling calves and grazing yearlings but also for finishing cattle to cover the first 2 to 3 months on feed when energy intake may be limited by stress, diet adaptation, and so forth. Formulations containing at least 14 mg of E_2 (or 20 mg of E_2B) in combination with at least 120 mg of TBA are generally considered high potency. They typically are reserved for cattle consuming high-grain finishing diets at or near-maximum intake. Other implant formulations are considered to be of moderate potency, although there is considerable variation within this category. Moderate-potency implants are most appropriate for grazing and backgrounding cattle and finishing cattle requiring a conservative implant strategy for nutritional or marketing reasons. Heifers generally are implanted more "aggressively" (greater potency) than steers because of their greater propensity to fatten at lighter weights.

Plane of nutrition (ie, feed intake relative to the animal's maintenance requirement) can limit implant effect on growth. In the study of Prichard et al [29], response by suckling calves to implanting without creep feed was half that seen when creep feed was provided. This interaction was also evident in the grazing cattle data presented by Kuhl [26]. Added weight from a single estrogenic implant (120-day grazing period) increased from 1.4 to 18.2 kg/head as daily gain increased from 0.20 to 1.04 kg. There was no indication that estrogenic implant use was detrimental to performance when the plane of nutrition was very low, and implanting was probably justifiable when daily gain was as little as 0.3 kg. In the trial of Berg et al [30], a low-, moderate-, or high-potency implant was administered to Charolais heifers at

the beginning of a backgrounding phase in which they were fed to gain 1 kg/d. The heifers subsequently received a high-potency implant and finished on an 85% concentrate diet. Moderate- and high-potency implants did not improve growth rate or efficiency relative to a low-potency implant during the backgrounding phase or overall; however, quality grade (ie, intramuscular fat) was reduced dramatically.

Sex has little effect on prepubertal response to implants. Response is affected by gonadal hormone production after puberty. Implants that provide anabolic compounds complementary to endogenous hormones (ie, androgen for intact heifers, estrogen for intact males) or, in the case of gonad removal, replacement for endogenous hormones (ie, estrogen in ovariectomized heifers) result in the greatest performance improvement [25,31]. Supplemental androgens and estrogens (in addition to endogenous supply) improve performance but to a lesser extent.

Although there is considerable variability among trials, implant use in one phase of production seems, typically, to have little effect on performance in subsequent phases (Table 1). Increasing potency of subsequent implants was not necessary to avoid negative carryover effects in these trials.

Impact on carcass and beef characteristics

Aggressive use of implants can increase carcass weight 30 to 40 kg and rib eye area 3 to 7 cm^2 relative to nonimplanted cattle. Dressing percent and yield grade usually are affected little, if any, when fed to comparable compositional endpoints [32]. Implant use also has been implicated in reduction of marbling (intramuscular fat) and tenderness.

Morgan [33] reported that marbling score of cattle declined with increasing aggressiveness of the implant treatment imposed. Conservative implant treatments involving an androgenic or low-potency estrogenic implant reduced marbling approximately one tenth of a US Department of

Table 1
Summary of carryover effects of implant use on performance in subsequent phases of production[a]

	Production phase		
Implant used in:	Suckling		Grazing/background
Performance effect in:	Grazing/background	Finishing	Finishing
Trails[b]	15 (1)	28 (5)	28 (2)
Weight gain[c]	+1 (−6 to +10)	−1 (−9 to +8)	0 (−7 to +8)
Trials		7 (1)	14 (2)
Feed:gain[c]		+5 (+3 to +12)	0 (−7 to +7)

[a] Brikelo (C. Birkelo, PhD, unpublished data, 2001).

[b] Number of trials conducted followed in parentheses by number of trials with statistically significant differences.

[c] Average percent change in performance variable owing to implant use in previous phase followed in parentheses by the range in percent change among trials.

Agriculture (USDA) score compared with no implant. More aggressive implant treatments involving one or more high-potency estrogen/androgen combination implants reduced marbling by two tenths of a score or more. Associated reductions in percent of cattle graded as USDA quality grade "Choice" were on the order of 2% to 7% and 25% to 30% for conservative and aggressive treatments respectively. Suckling, weaning, and backgrounding implants did not reduce marbling [34]. Johnson et al [35] reported that steers that received a high-potency estrogen/androgen combination implant required 35 additional days to achieve the same marbling score as their nonimplanted counterparts. Administering a low-potency implant on arrival followed 50 to 70 days later by a high-potency implant has resulted, in some cases, in less marbling score depression than administering a high-potency implant on arrival [36]. Newer moderate-dose estrogen/androgen implants (eg, 80 mg of TBA plus 16 mg E_2) have shown promise in lessening marbling score depression while achieving performance responses close to those achieved with high-potency combination implants [37]. In countries where leanness and little marbling are most desirable, aggressive programs involving high-potency implants have been most effective in achieving desired carcass characteristics.

Results reported in the literature regarding the effect of feedlot-phase implanting on tenderness are highly variable. Nichols et al [38] found that only 3 of 19 studies reported statistically significant increases in shear force due to implanting. Only 3 of 13 studies reported statistically significant decreases in tenderness as determined by taste panel evaluation. No relationship between implant type or number and tenderness was apparent. In the study of Platter et al [34], although tenderness was reduced by backgrounding or finishing-phase implants, taste panel perceptions of tenderness were not different when corrected for differences in marbling. Achieving marbling score targets at slaughter is desirable in any case but also may provide insurance to the extent that implants may affect tenderness. Platter et al [34] also reported that suckling and weaning implants did not reduce tenderness.

Related issues

Replacement heifers

Two implants are approved for use in heifers intended to be kept as breeding herd replacements (36 mg of zeranol and 10 mg of E_2B plus 100 mg of progesterone). This method allows implanting of all heifer calves in a herd before selection of replacements so as to benefit from the heavier weight of those not retained. Impaired reproductive performance of retained heifers has been reported in some trials but not others. Implanting heifer calves at birth can reduce conception rate by as much as 40% to 50% [39] but has little effect, if any, when a single implant is administered at approximately 1 month of age or older [40]. Multiple implants increase the risk of depressed

conception rate [41]. Increasing the plane of nutrition can reduce the risk. Implanting heifers between approximately 2 months of age and weaning does not affect weaning weight of their first calves [42]. Additionally, there is general agreement that preweaning implants do not impair rebreeding as 2-year-olds [40].

Side effects

The "buller" syndrome (persistent riding of a steer by its pen mates) and vaginal prolapse have been associated with the use of implants. Implants of low potency and less estrogenicity are less likely to contribute to bulling. Steers implanted with 36 mg of zeranol had approximately half the bulling rate of those implanted with 20 mg of E_2B plus 200 mg of progesterone [43]. The buller rate for steers that received a high-potency estrogen/androgen combination implant on arrival was 9.93% but 5.06% when steers initially received a low-potency implant followed by the high-potency implant 70 days later [44]. Turgeon and Koers [45] reported that implanting heifers on arrival with an estrogen implant followed by a second estrogen implant 75 days later resulted in twice as many prolapses (0.65% versus 0.27%) as a single estrogen implant on arrival.

Melengestrol acetate

Melengestrol acetate (MGA) is a synthetic steroid derived from modification of progesterone. It has progestational and glucocorticoid activity [46] and is used to suppress estrus and promote growth and feed efficiency of feedlot heifers. Daily dose is 0.25 to 0.50 mg.

Physiologic and metabolic effects

MGA binds to the progestin receptor with greater than 5 times the affinity of progesterone and has 125 times the activity [46,47]. A dose of 0.50 mg/d increases the number and size of ovarian follicles, but follicle maturation, ovulation, corpus luteum formation, and estrus are inhibited. Plasma progesterone is decreased, whereas that of E_2 is increased to approximately 5 pg/mL, comparable to that found during early proestrus. It is assumed that elevated E_2 from the ovaries is the mechanism through which MGA elicits an anabolic effect. This presumption is supported by the fact that MGA does not increase the growth of ovariectomized heifers [46]. Additionally, MGA was reported to increase plasma IGF-1 concentration, in keeping with results seen with estrogen-based implants [48]. Expression of mRNA for the IGF-1 receptor was increased in liver and muscle and for androgen receptor in liver; however, GH and cortisol were reduced. McCroskey and Kiesling [49] reported that MGA lowered the metabolic rate of heifers. This finding could provide an explanation for the observation of Busby and Loy [50] that fewer

deaths during a severe heat wave occurred in heifers fed MGA compared with those receiving none.

Effects on performance

Based on a pooled analysis of six trials, Duckett et al [25] reported that feeding MGA improved daily weight gain and feed efficiency of nonimplanted heifers an average of 10% and 3%, respectively. MGA effects on daily gain tended to be additive with an androgen but not a high-potency estrogen/androgen combination implant. Androgen and combination implants tended to improve feed efficiency compared with MGA alone (5%), and implant response was not improved further by concomitant feeding of MGA. Additivity of MGA and androgens would be expected because of complementary mechanisms for affecting growth, as is the case for estrogen and androgen implants. MGA would be beneficial to heifers implanted with estrogen only to the extent that they could respond to amounts of estrogen above that supplied by the implant; however, heifers still could benefit from a reduction in riding and disruption of feed intake patterns that can occur when cycling [50].

MGA at concentrations normally fed to heifers has not been effective at improving gain or feed efficiency of steers [51] or prepubertal heifers [52]. Additionally, the growth response to MGA is influenced by plane of nutrition. Purchas et al [53] reported that Holstein heifer calves fed 4.5 kg/d of supplemental grain responded to MGA with increased growth rate, whereas those receiving 0.9 kg/d did not.

Impact on carcass and beef characteristics

MGA fed to nonimplanted heifers typically has had little or no effect on dressing percent or rib eye area [25], but rib fat thickness and yield grade are increased. Increased marbling has been reported in several trials, although differences were generally not statistically significant. No reports of decreased marbling due to MGA were found in the literature. When fed to implanted heifers, a tendency toward greater fatness or quality grade is not apparent. Less cycling may reduce the number of dark-cutting carcasses at slaughter.

Purchas et al [53] reported a tendency for lower shear force in nonimplanted Holstein heifers fed MGA. This effect, along with increased marbling scores, also was noted by Busby et al [51] in both heifers and steers fed MGA and implanted with estrogen implants.

Zilpaterol

Zilpaterol belongs to a class of compounds known as β-adrenergic agonists. These phenethanolamine compounds bind to and positively

stimulate the β-adrenergic receptors through which the catecholamines epinephrine and norepinephrine function. Zilpaterol is provided as zilpaterol hydrochloride, in dry premix form, for addition to diets. Recommended daily dose is 0.15 mg/kg body weight.

Physiologic and metabolic effects

β-agonists have been researched extensively in recent years (see reviews by Beerman [54] and Mersmann [55]), although little has been published addressing zilpaterol specifically. β-agonists are water-soluble and rapidly absorbed from the digestive tract. Zilpaterol plasma concentrations increase rapidly, within 2 days of feeding. Maximum concentrations occur within 10 to 30 days [56].

Three types of β-agonist receptors have been identified (β_1, β_2, and β_3). They are present in most cell types, but numbers vary among species and tissues within species. Additionally, some compounds are more specific for one type of receptor than another. As a result, effects on growth can vary widely among β-agonists and among tissues. Zilpaterol functions mainly through the β_2 receptor [56]. In cattle, the β_2 receptor predominates in skeletal muscle and adipocytes. Intracellular actions are mediated through cyclic AMP and its activation or deactivation of key enzymes. Evidence suggests that indirect mechanisms (eg, through GH/IGF-1, thyroid hormones, and so forth) are not involved significantly [57], unlike steroidal compounds used in implants. β-agonists increase heart rate, dilate blood vessels, and decrease blood pressure. Amino acid uptake by muscle cells is increased, as is cell concentration of mRNA for myofibrillar proteins. Protein synthesis rate in muscle is increased, although this effect seems to be a short-term, transient phenomenon. Protein degradation rate is reduced, possibly through inhibition of calpastatin effects on proteases. The net effect is increased protein accretion and muscle cell hypertrophy. Increased glycogenolysis in muscle, increased lipolysis, and decreased lipogenesis in adipocytes, coupled with increased blood flow, seem to reflect a concerted effort to direct nutrients in support of enhanced protein accretion. Length of β-agonist effect apparently is limited by desensitization or down-regulation of receptors in response to long-term treatment.

Effects on performance

A review of 17 trials conducted in Mexico and South Africa [56–58] indicates that effects of zilpaterol on growth and efficiency are similar to those reported for other β-agonists. Bulls, steers, and heifers responded similarly. Daily live weight gain and efficiency were improved 14% to 25% and 8% to 26%, respectively. Feed intake was reduced in 7 comparisons and increased slightly or not affected in 11, with a mean reduction of only 2%.

In most trials, cattle were implanted with a high-potency estrogen/androgen implant. Zilpaterol and steroidal implants seem to be additive in improving weight gain and efficiency. Feeding zilpaterol for 50 days followed by a 2-day withdrawal did not result in significant improvement in performance over feeding for the final 30 days of the 50-day period. Weight gain and feed efficiency during a 14-day withdrawal of cattle treated with zilpaterol for the previous 49 days were not different from control cattle not previously fed zilpaterol. Recommendations have been to feed zilpaterol during the last 30 to 50 days before slaughter.

Impact on carcass and beef characteristics

In the 17 trials reviewed, dressing percent consistently was increased an average of 2.7%. As a result, zilpaterol's effect on carcass weight gain during the time period of treatment was even greater than on live weight gain. Additionally, Plascencia et al [58] reported that yield of subprimal cuts as a percentage of carcass weight was increased by zilpaterol. Marketing in a manner that takes into account additional carcass weight and yield would be necessary to fully benefit economically from the use of zilpaterol.

There was at least a trend in most trials toward reduced rib fat thickness and number of carcasses classified as overly fat because of zilpaterol use. Marbling was reduced significantly in only two of eight trials; however, marbling was, in general, low in these trials with or without treatment, equivalent to the mid-slight US Department of Agriculture marbling score. Shear force was tested in only one trial, and although zilpaterol treatment increased shear force (decreased tenderness) 19%, the difference was not significant.

Ionophore antibiotics

Ionophores such as monensin, lasalocid, laidlomycin, and salinomycin selectively inhibit ruminal microorganisms, thereby altering fermentation efficiency and end products available for absorption and performance [59,60]. Ionophores are lipophilic, carboxylic acid polyether compounds possessing a "cavity" created by the position of polar regions in the molecule that enhance entrapment of cations. Affinity for cations varies among ionophores. Monensin has greater affinity for Na^+ than K^+. Lasalocid has greater affinity for K^+ than Na^+ and even can accommodate divalent cations such as Ca^{++} in the cavity formed between two ionophore molecules. Ionophores alter cation flux across microbial cell membranes by creating a lipophilic ionophore–cation complex, which becomes solubilized in the lipid bilayer membrane. There the cation is exchanged for a proton, or as also can be the case with lasalocid, divalent Ca^{++} for two K^+. Transmembrane cation gradients (most notably Na^+ and K^+) are dissipated, and intracellular pH is

reduced. Affected microorganisms expend additional energy trying to maintain gradients and pH, reducing energy reserves below that needed to maintain a viable rumen population. They also may succumb to reduced pH. Gram-positive bacteria are most susceptible.

Physiologic and metabolic effects

Monensin and lasalocid alter nutrient digestion. In the studies reviewed by Spears [61], monensin and lasalocid increased apparent nitrogen digestibility approximately 3.5 percentage points, on average. Ruminal bacteria that normally use amino acids and peptides as energy sources are inhibited. A greater proportion of the nitrogen reaching the small intestine is in the form of feed protein, which typically is more digestible than that of bacteria. Reduced ruminal starch digestion was offset by increased digestion in the lower gut. Ionophore effect on fiber digestion was often positive. Energy digestibility was increased approximately two percentage points with monensin or lasalocid. Similar effects on nutrient digestion also have been reported for salinomycin [62] and laidlomycin [63].

Ionophores alter ruminal fermentation patterns. Molar proportions of the volatile fatty acids acetate and propionate are decreased and increased, respectively, by feeding monensin in concentrate and forage diets [60]. The ratio of acetate:propionate can be reduced by one third or more. Similar results have been reported for lasalocid [64] and salinomycin [65]. Methane is a byproduct of microbial conversion of glucose to acetate. A lower acetate:propionate ratio indicates less feed energy lost as methane. Methane accounts for 2% to 12% of feed gross energy consumed, with high-concentrate (ie, $>80\%$) diets typically below 5% and forage diets found in the higher end of the range [66]. Direct measurement of methane production demonstrated 25% and 15% reductions by inclusion of monensin in high-concentrate and forage diets, respectively [67,68]. Bacteria that produce the substrates for methane synthesis (H^+ and formante) are inhibited by monensin, whereas those that produce propionate are resistant.

Ionophores can reduce occurrence and severity of acidosis. Monensin and lasalocid inhibit lactic acid–producing bacteria, including the major producers, *Streptococcus bovis* and *Lactobacillus* species, while not inhibiting major lactic acid–using bacteria [69], thereby ameliorating ruminal pH and lactic acid concentrations [70]. Additionally, ionophores can alter eating behavior (ie, reduced eating rate and meal size), so as to reduce the rapidly fermentable substrate load present in the rumen [71,72]. Erratic feed intake is associated with subacute acidosis. Monensin reduces concentrate diet intake variation among individual animals within a day as well as day-to-day variation of individual animals [73]. Deaths due to digestive disorders (ie, acidosis, bloat, enterotoxemia, and coccidiosis) also appear to be reduced [74], presumably as a result of reduced intake variation. Reduced

variation also has been reported for laidlomycin; however, ionophores have not reduced occurrence of liver abscesses [75]. Monensin and lasalocid reduce bloat by reducing rumen fluid viscosity [76,77].

Impact on performance

The most consistent effect of ionophores is the improvement of feed efficiency. Intake is either reduced somewhat or not affected. Weight gain is either not affected or increased.

Goodrich et al [78] reviewed 228 published studies in which monensin effects on performance were tested. They reported that monensin (average dose, 246 mg/d; 32 mg/kg dry matter [DM]), reduced DM intake of feedlot cattle 6.4% but improved daily gain and feed efficiency 1.6% and 7.5%, respectively. Responses were dependent on dietary concentrations of monensin and metabolizable energy (ME). As monensin concentration increased from 0 to 44 mg/kg DM, intake decreased 9.9%. Greatest depressions occur early in the feeding period and, as a result, a reduced concentration (eg, one half of final concentration) often is used initially to allow for adaptation. Daily gain was increased slightly at low ($\leq$11 mg/kg DM) but not higher concentrations. Feed efficiency improved with increasing monensin concentration up to approximately 33 mg/kg DM, at which it was 8.7% better than controls. Greatest improvement in feed efficiency was achieved at a dietary ME concentration of 2.9 Mcal/kg DM. Intake depression decreased with increasing ME concentration. In a more recent summary of 46 studies conducted between 1984 and 1994 [79], monensin (average dose, 253 mg/d; 29 mg/kg DM) reduced intake only 2.7%. Daily gain was unaffected, and feed efficiency was improved 3.7%. The greater ME concentration of feedlot diets used in the more recent studies likely accounts for differences between results of this review and that of Goodrich et al [78].

Lasalocid and laidlomycin affect DM intake of feedlot diets to a lesser extent than monensin. Vogel [79] reported that lasalocid (23 studies; average dose, 277 mg/d; 29.2 mg/kg DM) reduced intake only 1.3%. Laidlomycin had no effect (38 studies; 87 mg/d; 8.4 mg/kg DM). Lasalocid and laidlomycin affected daily gain and feed efficiency similarly. They improved daily gain 3.7% and 4.9% and feed efficiency 4.7% and 4.5%, respectively. In a separate review of 10 studies (Birkelo, PhD, unpublished data, 2003), intake was, on average, unaffected by salinomycin at concentrations between 12 and 24 mg/kg DM. Daily gain and feed efficiency, however, were improved 5.1% and 5.5%, respectively.

Ionophores also have been effective in cattle on pasture, hay, and crop residues. Goodrich et al [79] reported that monensin (24 studies; average dose, 155 mg/d) increased daily weight gain of grazing stocker cattle 13.5%. Potter et al [80] fed green chopped grass/legume pasture and found that, in addition to improved weight gain, feed intake was reduced and efficiency

was improved by monensin, with an optimal dose of approximately 200 mg/d. Similar results have been reported for other ionophores [65].

Impact on carcass characteristics

Ionophores generally have had little or no effect on carcass characteristics such as marbling score and yield grade (eg, as reported in the studies of Merchen and Berger [81] and Zinn et al [82]). Effects that have been noted are most likely the result of altered weight gain rather than ionophore effects per se (see Clary et al [83]).

Non-ionophore antibiotics

Non-ionophore antibiotics from several chemically diverse groups are used to increase rate and efficiency of growth in cattle and include macrolide (tylosin), peptolide (virginiamycin), polypeptide (bacitracin), phosphoglycolipid (bambermycins), and tetracyclines (chlortetracycline and oxytetracycline). Although structurally different, they are effective mainly against gram-positive bacteria, with the exception of the tetracyclines, which are broad spectrum. Antibacterial effects are elicited primarily through one of two mechanisms [84–86]. The tetracyclines tylosin and virginiamycin interact with ribosomes of affected cells to inhibit protein synthesis. Bacitracin and bambermycins inhibit cell wall formation by preventing synthesis of component peptidoglycan strands that can make up 40% to 90% of the cell wall.

Physiologic and metabolic effects

In some studies, non-ionophore antibiotics have elicited changes in ruminal volatile fatty acid patterns (ie, increased propionate concentration, decreased acetate:propionate ratio, decreased methane production) similar to those of ionophore antibiotics, which also inhibit gram-positive bacteria [86]. When fed at levels necessary for growth promotion, however, more often than not they have had little effect [87,88]. Tylosin and virginiamycin inhibit lactate production and declines in ruminal pH [88]. *Streptococcus bovis*, a principal lactate producer, is susceptible to tylosin, virginiamycin, and, to a lesser extent, the tetracyclines and other antibiotics [89].

Effects of non-ionophore antibiotics on total tract, apparent digestion have been variable. Chlortetracycline has been reported in some studies to decrease diet digestibility, but in others to have no effect. Bambermycins had no effect on digestibility of forage diets but increased digestibility of concentrate diets 7% [90,91]. Feed protein degradation was reduced slightly, as was microbial protein synthesis, but amino acid supply to the small intestine was increased. Such a protein-sparing effect has been suggested for virginiamycin [92] but was not found when chlortetracycline was fed [93].

Data regarding metabolic effects of non-ionophore antibiotics in ruminants are limited. Rumsey et al [94] reported that feeding chlortetracycline at 350 mg/d to growing steers decreased pituitary gland sensitivity to thyrotropin-releasing hormone and growth hormone–releasing hormone. Thyroxine and GH secretions, in response to releasing hormone challenge, were reduced. Immunogenic bacteria in the intestine cause low-level inflammation and increase metabolic activity and energy requirements. Reduction in their numbers may decrease energy consumption by the gut; energy that, in turn, would be available for growth. In fact, intestinal epithelial cell turnover is slower and maintenance energy requirement is lower for specific-pathogen-free animals than those with normal gut flora [95]; however, direct evidence linking non-ionophore antibiotic feeding and reduced metabolic rate in cattle seems lacking.

Liver abscesses are common in cattle fed high-concentrate diets. A severely abscessed liver is associated with reductions of as much as 10% to 20% in rate and efficiency of growth. In a summary of 40 trials (6971 steers and heifers), Vogel and Laudert [96] reported a 73% reduction in incidence of liver abscesses in cattle fed 50 to 100 mg of tylosin phosphate per day. Brown et al [97] reported that chlortetracycline fed at 70 mg/d was approximately one third as effective as tylosin fed at 75 mg/d. In the combined results of four trials (1360 steers and heifers), virginiamycin reduced total abscessed liver incidence 39% [85].

Impact on performance

The effects of chlortetracycline and oxytetracycline on performance of growing and finishing cattle have been reviewed extensively [98]. Improvements of 7% for daily gain and 5% for feed efficiency were reported for chlortetracycline (~70 mg/d) compared with no antibiotic (236 trials). Improvements of 3% for both daily gain and feed efficiency were reported for oxytetracycline (~75 mg/d; 47 trials). Responses were affected by plane of nutrition. On average, rate and efficiency of weight gain were improved 5% and 4%, respectively, by chlortetracycline for cattle gaining 1 kg/d or more; however, improvements of 9% and 5% were reported for cattle gaining 0.7 kg/d or less. Similar differences were found for oxytetracycline.

Vogel and Laudert [96] summarized the results of 40 feedlot-finishing trials and reported that tylosin (50–100 mg/d) did not affect feed intake but improved daily gain and feed efficiency 2.1% and 2.7%, respectively, compared with no antibiotic. Virginiamycin (165 mg/d) also was reported to have little effect on intake, but daily gain and efficiency were improved 3.0% and 3.8%, respectively (seven trials) [85]. Improvements of 3.6% for daily gain and 2.6% for feed efficiency were reported for bambermycins fed at 20 mg/d in growing and finishing diets (nine trials) [99,100].

Improvements in daily gain of grazing cattle due to non-ionophore antibiotic feeding have varied widely. Daily gain response to bambermycins

(up to ~20 mg/d) averaged 11.7% in 14 trials but varied from 2.3% to 24.0% (eg, Keith et al [101]). Corah et al [102] reported a 15.3% increase in daily gain of steers receiving chlortetracycline (average, 437 mg/d) in a free-choice mineral mix while grazing brome grass pastures. Brazle et al [103] found that weight gain of heifers fed oxytetracycline at 422 mg/d increased 20.7% while grazing native tallgrass. Chlortetracycline provided in a free-choice mineral supplement (average intake, 869 mg/d per cow-calf pair) increased daily gain of both cows (47%) and suckling calves (8%) [104]. In other studies, chlortetracycline and oxytetracycline have resulted in little or no improvement [104–106]; however, in these studies, fewer cases of pinkeye and foot rot often were noted.

Impact on carcass characteristics

Vogel and Laudert [96] reported that dressing percent of cattle fed tylosin was 2.4% greater than that of cattle not fed tylosin (61.80% versus 61.65%). Liver abscess rates for the two groups were 27.90% and 7.48%, respectively. Rumsey et al [93] suggested there was a tendency for chlortetracycline-fed cattle to be fatter than those not receiving the antibiotic. A similar trend was seen in a summary of three trials involving yearling steers fed virginiamycin [107]; however, non-ionophore antibiotics generally have had little effect on carcass characteristics.

Direct-fed microbials and enzymes

Direct-fed microbial products (DFMs; also referred to as *probiotics*) contain viable bacteria, yeast, or molds. They also may contain the medium on which the microorganisms were cultured or extracts of the culture. Initial attention was directed toward use in stressed cattle as an aid in re-establishment of normal gastrointestinal microflora and reduction in stress-related illness; however, continuously fed DFMs can enhance rate and efficiency of growth in healthy, nonstressed cattle as well. Examples of commonly used bacteria include those from the genera Lactobacillus (eg, *L. acidophilus*), Propionibacterium (eg, *P freudenreichii*) and Streptococcus (eg, *S faecium*). The fungal microorganisms *Saccharomyces cerevisiae* (SC) and *Aspergillus oryzae* (AO) are commonly used species of yeast and molds, respectively. Products often contain multiple species of bacteria and fungi. More detailed reviews include those of Fuller [108], Kung [109], and Newbold [110].

Enzymes are proteins that catalyze chemical reactions. Supplemental enzymes enhance breakdown of feed fractions and increase potentially absorbable nutrient supply. They are substrate-specific, and often, several different enzymes must work together to break down complex chemical structures that make up feed fractions (eg, fiber). Enzyme use in ruminant diets recently has been reviewed by Beauchemin et al [111] and Kung [112].

Effects of DFMs and enzymes on gut function and performance of cattle vary considerably among studies. Bacteria and fungi used in DFM products vary by genus and species and also by strains selected for specific traits. Quantity and viability vary as well. Most products contain multiple types of microorganisms or enzymes, the potential interactions of which are understood poorly. Products used in published studies are typically not well defined. Considerable variation among studies seems inevitable, and separating the effects of different types of microorganisms from product-specific effects is difficult.

Physiologic and metabolic effects

The greatest effect of DFMs on cattle performance is believed to be through altered rumen metabolism. General lack of persistence of microorganisms introduced into the rumen necessitates continuous feeding to maintain changes [113,114].

In some studies, bacterial DFMs have reduced lactic acid accumulation, stabilized ruminal pH, or promoted a more efficient fermentation pattern, with a shift toward greater propionate production. For example, Van Koevering et al [115] fed a lactate producer, *Lactobacillus acidophilus* (LA), to cannulated steers consuming a 92% concentrate (rolled corn) diet. LA decreased ruminal lactate concentration and tended to increase pH and feed intake. Total tract digestibility of DM, starch, and protein was not improved. Introduction of lactate-producing bacteria may cause ruminal flora to adapt to the presence of lactate, making them more capable of metabolizing lactate in the event of a challenge [116]. Greater ruminal protozoa numbers in steers fed LA also could have contributed to higher pH and lower lactate through their accumulation of carbohydrate and possible delaying of fermentation. Bacteria that use lactate and produce propionate also may alter rumen metabolism favorably. Kim et al [117] found that feeding *Propionibacterium* (PB) *acidipropionici* reduced acetate:propionate but had no effect on lactate or pH. The combination (LA plus PB) also reduced the acetate:propionate ratio.

Fungal DFMs increase bacterial populations, most notably the fiber digesters, which in turn can increase rate, although not always extent, of fiber digestion and microbial protein production and flow to the small intestine. Some ruminal microorganisms are sensitive to even the low levels of oxygen (0.5%–1.0%) present in what is considered an anaerobic environment. The ability of yeast preparations to scavenge oxygen in the rumen has been correlated to their ability to stimulate rumen bacterial growth. Additionally, dicarboxylic acids (malate and fumarate) produced by fungi stimulate lactate uptake by ruminal lactate–using bacteria. Enhanced lactate uptake may contribute to a higher ruminal pH, a condition particularly beneficial to fiber-digesting bacteria. Preparations based on the mold AO elicit effects similar to yeasts, except that they are incapable of

scavenging oxygen. Some of the enzymes they contain are complementary to those produced by ruminal microorganisms. Ferulic and coumaric esterases may be particularly helpful by breaking ester bonds between lignin and plant cell wall carbohydrates, making the latter more digestible. SC and AO have been reported in some studies to increase total tract diet digestibility but not in others (eg, Firkins et al [118], Mir and Mir [119], and Wiedmeier et al [120]). Vitamins and unidentified growth factors often are mentioned as potential contributors of fungal DFMs to improved performance; however, little direct evidence is available.

Postruminal effects of DFMs are likely similar to those suggested for the lower gut of nonruminants. Bacterial DFMs have increased intestinal lactobacilli in calves [121,122]. SC does not colonize the rumen but passes into the lower tract, with a significant proportion of the yeast cells maintaining viability [113]. Numbers of detrimental bacteria in the intestine may be reduced by DFMs in two ways. Direct-fed bacteria can compete for attachment sites in the gut or nutrients (competitive exclusion), reduce pH, or produce antibacterial compounds [108]. Yeast, on the other hand, contains an indigestible cell wall constituent, mannan oligosaccharide, to which some gram-negative pathogens (eg, *Salmonella typhimurium*) adhere, reducing colonization of the intestinal epithelium and facilitating their removal from the digestive tract [123]. As with antibiotics, reduction of immunogenic bacteria is believed to decrease energy consumption by the gut.

Concern over degradation in the rumen has hindered acceptance of enzymes in ruminants [124]; however, Morgavi et al [125] found several enzyme products fairly stable when incubated in rumen fluid for up to 6 hours and pancreatin or pepsin for 1 hour. Enzyme source and type seem to be significant contributors to variation in resistance to degradation and, no doubt, efficacy. At recommended application rates, exogenous enzymes probably increase digestion relatively little through direct hydrolysis; however, Morgavi et al [126] demonstrated synergy between exogenous fibrolytic enzyme preparations and a mixed enzyme preparation derived from ruminal microorganisms. Hydrolytic capacity for combinations of exogenous and endogenous enzyme preparations were 20% to more than 100% greater than would be expected from the weighted average of the preparations used separately. The nature of the synergy is not known. Feng et al [127] reported treatment of smooth brome grass hay with an enzyme preparation containing predominantly cellulase and xylanase activities increased total tract digestibility of DM and fiber fractions (neutral detergent fiber and acid detergent fiber) 8.5%, 8.9%, and 13.1%, respectively. Ad libitum DM intake was increased 11.8%. Fibrolytic enzymes have been beneficial in concentrate diets as well. Zinn and Ware [128] reported improved performance of steers fed diets containing 11% to 22% ground sudan or sudan plus alfalfa hay with flaked sorghum or corn grain and a commercial cellulase/xylanase product top-dressed at the time of feeding. They concluded that improved performance was primarily attributable to

increased intake resulting from enhanced digestion of fiber that, even at the relatively low levels found in finishing diets, had the potential to restrict intake when roughage digestion was low (ie, <30%). Krause et al [129] reported that in vitro DM digestibility of steam-flaked sorghum grain was increased by enzyme treatment; however, in a subsequent study, Richardson et al [130] found no increase in in vivo DM or starch digestibility but did report increased crude protein digestibility and nitrogen retention.

Impact on performance

Studies in which positive effects of microbial products have been reported indicate that performance responses are similar in magnitude to those elicited by ionophores. Swinney-Floyd et al [131] reported that PB plus LA improved feed efficiency 3.9% in calves fed a corn-based finishing diet without ionophores or antibiotics. Neither daily gain nor intake were affected. Huck et al [132] found that LA fed during the step-up phase when grain intake was increased (days 1–28) followed by PB or PB during step-up followed by LA increased gain 4.9%. The former (LA/PB) also improved feed efficiency 5.6%. Intake of the 84% flaked and high-moisture corn diet, which included monensin and tylosin, was not affected. Others also have reported 5% to 7% improvements in gain and 0% to 5% improvements in feed efficiency with unchanged intake [133]. Trenkle [134] found that LA and PB had no effect on intake, gain, or efficiency when added to a 50% wet-corn gluten feed–finishing diet. He suggested that the low risk of acidosis posed by such a diet reduced the likelihood of a response to bacterial DFMs, the proposed mode of action of which is, in part, to reduce ruminal lactic acid concentration and to stabilize pH. Explanations for lack of effect in other trials (eg, Klopfenstein et al [135]) are not readily apparent.

Improved performance has been reported for backgrounded calves and finishing cattle when they are fed SC and AO. For example, Birkelo and Berg [136] reported that SC increased gain of yearling steers 4.3% when fed an 84% rolled corn–based finishing diet with monensin for 95 days. Intake was not affected. Efficiency improvement (3.7%) was not statistically significant. Hinman et al [137] found a similar response to SC in steers fed barley/potato byproduct–finishing diets for 115 days. Yeast increased gain 6.9% and increased efficiency 4.5%. Intake was not affected. In contrast, no benefit was found in yearlings fed a 100% concentrate whole-shelled corn finishing diet or calves backgrounded on a limit-fed 69% high-moisture corn diet [138,139]. It may be that these situations, if not well controlled, have the potential to overwhelm the ability of yeast to ameliorate ruminal lactic acid concentration and pH.

Dhuyvetter et al [140] reported that AO increased gain of backgrounded heifer calves 4.9% and increased efficiency 6.0% when included in a 63% corn silage/oat hay diet. Intake was not affected. Others have reported no performance response (eg, Kreikemeier and Varel [141]).

Positive effects on performance of growing cattle have been reported for both fibrolytic and amylolytic enzyme preparations [129,142,143]. Increased daily gain is the most consistent response, ranging from approximately 6% to 10%. Intake and efficiency responses, on the other hand, vary considerably, with several studies reporting no effect, whereas others indicate improvements of up to 6% and 11%, respectively. Complete lack of effect also has been reported (eg, Kesson et al [144]).

Impact on carcass and beef characteristics

Most studies indicate no effect of DFMs or enzymes on carcass characteristics beyond those that might be associated with heavier carcass weights resulting from a positive growth response (eg, Hinman et al [135] and Galyean et al [131]).

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