GROWTH REGULATORS, ANIMAL

1. Introduction

The growth of animals can be defined as an increase in mass of whole body, tissue(s), organ(s), or cell(s) with time. This type of growth can be characterized by morphometric measurements; eg, skeletal muscle or adipose tissue growth can be described by observing temporal changes in cell number, ie, hyperplasia, and cell size, ie, hypertrophy. Growth also includes developmental aspects of function and metabolism of cells and tissues from conception to maturity.

Both types of growth are influenced by genotype, nutritional status, and gender of the animal. Studies conducted in the early 1900s described how these factors influenced allometric growth of tissues, through dissection or proximate composition measurements. Development of histological and histochemical methods allowed animal scientists to characterize cellular aspects of tissue growth, but other methods were needed to determine the mechanisms by which cell number or size were controlled. Within groups of animals that share similar genotype, nutritional regimen, or gender, differences in metabolic hormone concentrations and/or action bring about differential regulation of proteins (qv), lipid, carbohydrates (qv), and mineral metabolism (see MINERAL NUTRIENTS). These differences influence how consumed nutrients are used by growing animals. Change in partitioning of nutrients occurs coincident with normal allometric growth from birth to mature size. When animals are offered diets ad

libitum (to appetite) the proportion of nutrients used for lipid accretion increases from birth to sexual maturity, or from birth to normal market weight or mature size, unless energy intake is restricted. This change is influenced by metabolic hormone action; rarely do any of the hormones or other influencing factors act independent of each other to regulate nutrient partitioning. Complex interactions allow for integration of influences to accommodate a coordinated chronic regulation of nutrient use for maintenance or growth so that an animal may adapt to its environment (see FEEDS AND FEED ADDITIVES, NONRUMINANT FEEDS; FEEDS AND FEED ADDITIVES, RUMINANT FEEDS).

Improved understanding of the control of metabolic aspects of growth has provided the opportunity to regulate animal growth. Improvement of rate and efficiency of growth benefits the producer. Improvement in composition of meat animals benefits the producer through more efficient gain and greater value, and benefits the processor through less labor requirement for trimming and removal of fat. The consumer benefits by receiving a quality, desirable food at a cost reflective of efficient production.

Four general classes (ca 1993) of growth regulators are approved by the Food and Drug Administration (FDA) for use in food-producing animals in the United States. These include naturally occurring and synthetic estrogens and androgens, ie, anabolic steroids (qv); ionophores; antibiotics (qv); and bovine somatotropin. Compounds in the first class, anabolic steroids, act as metabolism modifiers to alter nutrient partitioning toward greater rates of protein synthesis and deposition, thereby increasing the weight at which 25 to 30% lipid content in the body or carcass is achieved. Ionophores have highly selective antibiotic activity and appear to enhance feed conversion efficiency through effects on ruminal microbes. Antibiotics, administered at subtherapeutic doses, enhance growth through improving feed conversion efficiency and/or growth rate, with no consistent effect on body or carcass composition.

Two other classes of growth regulators, ie, somatotropin or somatotropin secretogogues, and select synthetic phenethanolamines, have been investigated for the ability to alter growth. In 1993, the FDA approved administration of recombinant bovine somatotropin for increasing milk production in dairy cows (see GENETIC ENGINEERING, ANIMALS). One phenethanolamine, ractopamine, was approved by the FDA in December, 1999, for use in finishing pigs. The commercial name of the ractopamine product, produced by Elanco Animal Health, is Paylean. Administration of native or recombinant somatotropin (ST) to growing pigs, cattle, and lambs dramatically enhances rate, efficiency, and composition of gain. Likewise, experimental dietary administration of select synthetic phenethanolamines, most of which are β-adrenergic agonists, also has produced striking changes in rates of skeletal muscle and adipose tissue growth and accretion in growing cattle, lambs, pigs, and poultry.

Somatotropin, the β-adrenergic agonists, and the anabolic steroids are considered metabolism modifiers because these compounds alter protein, lipid, carbohydrate, mineral metabolism, or combinations of these; and they partition nutrient use toward greater rates of protein deposition, ie, muscle growth, and lesser rates of lipid accretion. Historical data leading to understanding of the mechanism(s) of action are found in reviews on anabolic steroids (1), somatotropin (2–4), and the phenethanolamines (5–7).

2. Anabolic Steroids

Naturally occurring and synthetic estrogens and androgens have been extensively and safely used to improve efficiency and carcass composition in growing beef cattle in the United States since the early 1950s. Several anabolic steroid implants have been approved for use in beef cattle in the United States, but only one, zeranol [55331-29-8], is approved for use in lambs. Anabolic steroids are not used for growth regulation in swine or poultry (see STEROIDS).

Commercial products approved by the Food and Drug Administration include the naturally occurring hormone estradiol [50-28-2] (Compudose) (**1**); the natural hormone progesterone [57-83-0] (**2**), used in combination with estradiol or estradiol benzoate, ie, Steer-oid, Synovex-S and Synovex-C for calves; the fungal metabolite zeranol [55331-29-8] (Ralgro) (**3**) which has estrogenic properties; the synthetic progestin melengestrol acetate [2919-66-6] (MGA) (**4**); testosterone (**5**) propionate [57-85-2] in combination with estradiol benzoate, ie, Synovex-H or Heifer-oid; and a synthetic testosterone analogue, trenbolone acetate [10161-34-9] (TBA) (**6**) which is used alone, ie, Finaplix, or in combination with estradiol, ie, Revalor. Structures of these anabolic steroids are shown in Figure 1.

Classification of the anabolic steroids is based on chemical structures and associated actions. A review of the biosynthesis and metabolism of the naturally occurring estrogens and androgens is available (1). Names, descriptions, approval dates, and recommended doses of the commercial products are found in References (1,8), and (9). Although steroids may be orally active, the FDA approved mode of administration is the subcutaneous implant. Effective dose is lower with implant rather than oral administration.

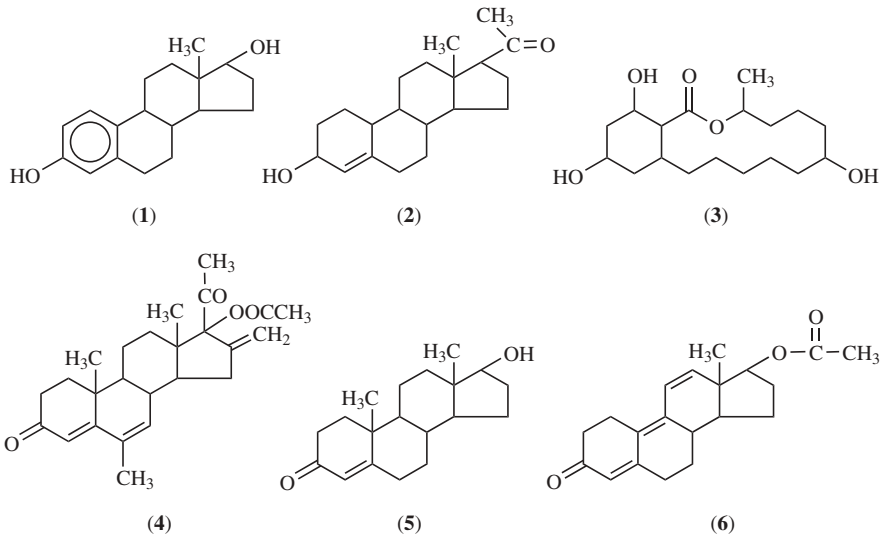

Fig. 1. Chemical structure of naturally occurring and synthetic sex steroids used in commercial anabolic steroid implant preparations.

Efficacy of these anabolic steroid implants has been summarized (1,8–12). Growth responses to anabolic steroids vary greatly, ranging from no response in feedlot bulls (13) to a 69.9% increase in average daily gain in heifers treated with trenbolone acetate (14). The choice of anabolic steroid depends on gender. The estrogenic compounds are generally more effective in steers. The response of females to both estrogens and androgens is more variable and less consistent, but superior responses are seen using the androgenic steroids. Use of a combination of anabolics generally produces an additive response compared to use of either estrogenic or androgenic implant alone. Response in bulls is generally less than that of steers, and implanted steers often achieve the growth performance observed in nonimplanted bulls (15).

2.1. Growth Performance Response. The consistent net effect of anabolic steroid implant use in growing ruminants appears to be increased rate of protein and live weight gain, and increased live weight at which carcass or empty body fat concentration equals that in nonimplanted cattle; thus increasing their potential mature size. Increased feed intake is frequently observed.

Rate of live weight gain is increased 10 to 20% on average with the use of anabolic steroids. Responses approaching 50% have been observed in lambs implanted with a combination of 35 mg trenbolone acetate (TBA) plus 5 mg estradiol-17β (16), and in beef steers housed in metabolism chambers and implanted with a combination of 140 mg trenbolone acetate and 20 mg estradiol-17β (17). Young animals may respond better to steroid implants than older animals (18–21). Greater responses have been observed during the initial period following implantation, which may be caused by the declining circulating concentration of the anabolics after the first few weeks (8,17,22,23). Trenbolone–estradiol combinations appear to be superior to the use of either implant alone. Dose-response efficacy trials conducted for FDA approval of TBA–estradiol combinations indicate that the average daily gain (ADG) plateaued at a dose of 118 mg TBA plus 24 mg estradiol, but the feed efficiency plateaued at 139 mg TBA plus 28 mg estradiol (24). ADG increased 18% and the feed:gain ratio reduced 9.5%; both exceeded the response to 30 mg of estradiol alone. Implants of 140 mg TBA alone did not improve growth performance in this and other studies (23,25). A TBA–estradiol ratio of 5:1 appears to be optimum for feedlot steers fed a high grain diet.

Efficiency of feed use for growth is usually improved with anabolic steroids, but the magnitude of the response is somewhat variable. Improvements of 5 to 14% have been reported (26–30). Trenbolone–estradiol combinations decrease feed:gain ratios 10–13% (24,31–33). The degree of response is clearly influenced by changes in dry matter intake, which are also variable, and by the degree of change in composition of gain. The majority of studies in which large increases in gain are observed also result in 10% increases in intake (30) and proportional increases in lean mass in cattle (18) and lambs (16,34). However, no significant changes in intake were observed in several studies (13,35–37).

2.2. Composition of Gain Response. Few studies investigating the effects of anabolic steroids on growth in ruminants in the United States include the direct measurement of carcass or empty body composition necessary to understand the mode of action and to define nutrient requirements. Total carcass

lean, ie, muscle, increased 9.5 and 10.4% in steers implanted twice with 300 mg trenbolone acetate and 36 mg resorcylic acid lactone [26538-44-3] (Ralgro, Pitman-Moore) over the live weight range 250 to 400 kg (35). Separable fat was reduced two percentage points. Efficiency of gain was greater in implanted cattle fed at the higher of two levels of energy intake. Dressing percentage was higher in implanted cattle, which implies that neither organ weights nor gut fill were increased with treatment.

Long-term administration of trenbolone acetate and resorcylic acid lactone to heifers and steers fed to 491, 612, or 731 days of age exhibited greater absolute and relative amounts of carcass lean and lesser absolute and relative amounts of carcass fat than nonimplanted cattle (18). Sex-by-implant interactions were not significant. Cattle implanted the longest exhibited a greater increase in carcass lean than cattle implanted for shorter periods. The increase in carcass weight of implanted cattle was accounted for entirely by increase in carcass lean; decrease in fat accretion was offset by increased bone growth. Few studies on the effects of anabolic steroids in fed cattle have been conducted with degree of marbling as the end point. Growth performance and composition of gain responses to TBA–estradiol implants, compared in three breeds of steers representing different frame sizes, indicated little effect on carcass composition, carcass quality grade, or retail cut distribution (33). However, live weight required to reach the small degree of marbling end point was increased 25 to 45 kg using TBA–estradiol implant; fat gain was increased by 19% on average in these cattle. These results suggest that anabolic steroids stimulate growth without dramatic effects on composition of gain and increase the weight at which a common carcass or intramuscular fat concentration is achieved.

The consistent improvement in rate of protein deposition observed in growing ruminants indicates that anabolic steroid implants exert their primary influence through altering protein metabolism. There are lesser effects on lipid metabolism.

2.3. Mechanism of Action. Few data are available that describe the effects of anabolic steroids on protein metabolism; even fewer data exist for assessment of direct effects of anabolic steroids on lipid metabolism in growing ruminants. The lack of any consistent change in somatotropin, prolactin, insulin, or other metabolic hormones (qv) in a total of 15 studies has been noted (1,38).

Protein metabolism studies suggest that rates of fractional protein synthesis and protein degradation may be reduced by trenbolone acetate; degradation rates may be reduced to a greater extent in rats (39,40) and lambs (41,42) to increase protein accretion rate. Combined TBA–estradiol implant treatment increased daily live weight gain 50–60% at similar feed intakes, and increased daily nitrogen retention 100 and 146% in steers during the first seven weeks of treatment in two separate studies (17). Estimates of whole-body protein synthesis rate, based on metabolic body size, were similar throughout the 10-week experiment; amino acid oxidation was lower in treated steers at weeks two and five, compared to control animals. Urinary 3-methyl histidine excretion was slightly less and total energy retention was unaffected in treated steers, indicating that reduction of protein degradation rate may account for the bulk of the improvement in daily gain and nitrogen retention. Heat production was not increased in steers treated with the TBA–estradiol combination.

One possible mechanism responsible for the ability of trenbolone acetate to stimulate skeletal muscle hypertrophy may be through enhanced proliferation and differentiation of satellite cells as the result of increased sensitivity to insulin-like growth factor-I (IGF-1) and fibroblast growth factor (43).

Very little data are available regarding effects of anabolic steroid implants on the lipid metabolism in growing ruminants. Lipogenic enzyme activity and fatty acid synthesis *in vitro* were elevated in subcutaneous adipose tissue from bulls implanted with estradiol (44), which may account for the increase in fat content of carcasses reported in some studies. TBA implants have no effect on lipogenesis in intact heifers, and only tend to reduce lipogenic enzyme activities in ovariectomized heifers (45).

2.4. Economics. Estimates of anabolic steroid use in growing cattle indicate that savings associated with reduced feed costs are approximately $50.00 per animal. Increased value of the carcass resulting from the increased amount of saleable lean meat produced is estimated to range from $15.00 to $30.00 per animal.

Withdrawal from anabolic steroid treatment is not required before slaughter because residue levels in edible tissues are negligible, and are significantly lower than other sources of estradiol such as the normal endogenous production in humans and the phytoestrogens consumed in plant food sources (1).

3. Ionophores

An ionophore may be defined as an organic substance that binds a polar compound and acts as an ion-transfer agent to facilitate movement of monovalent, eg, sodium and potassium, and divalent, eg, calcium, ions through cell membranes (46). The change in electrical charge in membranes influences the transport of nutrients and metabolites across the cell membrane, but the exact mechanism by which ionophores improve growth performance in growing ruminants is not known. Several reviews of the proposed mode of action and efficacy of ionophores are available (46–52).

The FDA first approved use of a polyether ionophore as a feed additive for cattle in 1975. Ionophores were first isolated from bacteria generally of the *Streptomyces* genus, but are produced commercially by bacterial fermentation (qv). Monensin [17090-79-8] and other ionophores are being fed to over 90% of feedlot cattle grown for beef (53) to enhance efficiency of gain; improvements of 5–10% are common. Ionophores also are used as anticoccidial drugs in poultry production and have similar, but lesser, effects in ruminants (54).

Doses range from 6 to 33 ppm in the diet, but very little if any ionophore can be measured in the circulation after feeding. Monensin is absorbed from the gut, metabolized by the liver, and excreted into the bile and back into the gut. Thus tissue and blood concentrations are very low. Over 20 metabolites of monensin, which have little or no biological activity, have been identified (47,55).

3.1. Growth Performance Response. Ionophores consistently improve feed conversion efficiency in growing cattle. In many cases feed intake is reduced without changing the rate of weight gain. When feed efficiency is

improved, but intake is not changed, an increase in rate of weight gain is observed. Trials in which monensin was fed indicated that the gain-to-feed ratio increased 4–12%, rate of gain did not significantly increase (1.6%), and feed intake was reduced 6.4% (48). An examination of growth performance responses against monensin dose, for published data up to 1990, generally showed a similar response magnitude for rate and efficiency of gain (48,52). Effects on carcass yield as a percentage of live weight and on carcass composition were very small and of little economic importance in most cases.

Dietary administration of ionophores is coupled with the use of anabolic steroid implants to maximize rate and efficiency of gain in growing cattle. Effects of ionophores and anabolic steroid implants are generally additive.

3.2. Mechanism of Action. The positive effects of ionophores on growth performance in growing cattle have long been thought to result from changes in the digestive system, particularly those that occur in the rumen. Hydrogen production is reduced, which leads to reduced methane production and less energy lost in this form. A shift in fermentation products toward greater propionate and less acetate production, decreased ammonia production which may increase protein availability, and reduction of lactate-producing bacteria in the rumen to prevent rumen acidosis may all contribute to the increased efficiency of gain which occurs (52). Increased or improved amino acid composition of absorbed nitrogen could remove constraints on amino acid availability for protein synthesis, or could result in indirect effects on metabolic hormone secretion rates (56). Plasma concentrations of minerals are also altered upon feeding ionophores (57,58). The consequences of these changes are unknown. Other benefits of ionophores include maintenance of good general animal health through reducing the incidence or severity of legume and feedlot bloat (59), and pulmonary emphysema (60).

4. Antibiotics

Antibiotics used in livestock and poultry production improve growth rates and efficiency of gain. Subtherapeutic doses are used for these purposes, and effects are similar in magnitude to those achieved with ionophores in growing ruminants. However, antibiotics are efficacious in all livestock species and in poultry. Intermediate doses are used to prevent disease in exposed animals, and therapeutic doses are used to treat animals that are ill. Antibiotics, produced by microorganisms, and chemobiotics or chemotherapeutics, chemically synthesized, are drugs and therefore regulated by the Food and Drug Administration. Monitoring of proper use and avoidance of residues entering the human food chain is accomplished through joint monitoring and surveillance programs conducted by the FDA and the Food Safety and Inspection Services of the USDA. Certification programs among producer groups assure that appropriate withdrawal times and use guidelines are followed.

Antibiotics approved for use as growth enhancers in livestock and poultry include bacitracins, bambermycins, lincomycin [154-21-2], penicillin [69-53-4], streptomycin [57-92-1], tetracyclines, tiamulin [55297-95-5], tylosin [1401-69-0], and virginiamycin [11006-76-1] (61)

Table 1. **Benefits of Subtherapeutic Level of Antibiotic in Food-Producing Animals,[a] % Improvement**

Species	Number of experiments	Rate of gain	Feed/unit gain
pigs			
starter	378	16.1	6.9
grower	276	10.7	4.5
finisher	279	4.0	2.1
cattle			
calves	85	14.3	
feedlot	65	4.9	5.3
chicken			
broiler	286	2.9	2.5
layer hens	244	4.0[c]	4.7[b]
turkeys	126	7.0	3.8

[a]Refs. 61, 68 and 69.
[b]Egg production improvement; feed required per dozen eggs.

Chemically synthesized antimicrobials used in animal and poultry feeds include arsenicals, eg, arsanilic acid [98-50-0], sodium arsanilate [127-85-5], and roxarsone [121-19-7]; sulfa drugs, eg, sulfadimethoxine [122-11-2], sulfamethazine [57-68-1], and sulfathiazole [72-14-0]; carbadox [6804-07-5]; and nitrofurans, eg, furazolidone [67-45-8] and nitrofurazone [59-87-0].

4.1. Effects on Growth Performance. Effects of subtherapeutic use of antibiotics were documented as early as 1950 (62–65), and the efficacy in food-producing animals has been summarized (Table 1) (61,66–69). Effects in very young animals are greater than in older animals, presumably because significant benefits are achieved through inhibiting growth of bacteria that have adverse effects on growth. Conversely, effects are smaller when animals are exposed to environmental conditions that minimize exposure to pathogenic bacteria or that minimize stress and nutritional inadequacies.

4.2. Mechanism of Action. The mechanisms by which antibiotic administration at subtherapeutic levels enhance growth rate and efficiency of gain in growing animals have not been clarified. Possible modes of action include disease control, nutrient sparing, and metabolic effects. There is extensive evidence that the principal benefit from subtherapeutic use of antibiotics results from the control of harmful microorganisms.

Transport, intermingling of animals, and environmental stress can result in exposure to nonresident microorganisms or a greater predisposition to subclinical disease. The use of subtherapeutic levels of antibiotics can reduce this stress and result in improved, more cost-efficient production. The bacteriostatic or bacteriocidal effects are apparent in contaminated or previously used environments, where 5–10% improvements in growth rate or feed efficiency commonly are observed. Young animals in which the immune system is not yet fully developed also respond to a greater extent than older animals. Controlled experiments demonstrate that feeding antibiotics at subtherapeutic levels allows animals in these environments to perform closer to their genetic potential.

The nutrient sparing effect of antibiotics may result from reduction or elimination of bacteria competing for consumed and available nutrients. It is also

recognized that certain bacteria synthesize vitamins (qv), amino acids (qv), or proteins that may be utilized by the host animal. Support of this mode of action is found in the observed nutritional interactions with subtherapeutic use of antibiotics in animal feeds. Protein concentration and digestibility, and amino acid composition of consumed proteins may all influence the magnitude of response to feeding antibiotics. Positive effects appear to be largest when protein intake is insufficient or optimum amino acid composition of absorbed nitrogen is not present in order to achieve optimal rates of weight gain.

Evidence for consistent, positive metabolic effects of feeding antibiotics is fragmented and inconclusive. Direct measurement of increased uptake of nutrients, ie, *in vivo* amino acids, glucose, or volatile fatty acids in ruminants, have not been reported.

5. Somatotropin

Growth and metabolism of tissues in domestic animal species are influenced or regulated by several metabolic hormones. Insulin [9004-10-8], the thyroid hormones, and the catecholamines are all important in maintaining homeostasis through acute regulation of protein, lipid, carbohydrate, and mineral metabolism. However, somatotropin [9002-72-6] (growth hormone) exerts its influence in a chronic, coordinated way to regulate metabolism and somatotropic development and growth of principal tissues and organs in the body during postnatal growth (70). Normal somatotropin (ST) concentrations in the circulation are essential for normal growth. Exogenous administration of ST accelerates growth of several tissues through stimulation of cell proliferation and accumulation of deoxyribonucleic acid (DNA). The increases in circulating levels that result also repartition nutrient use toward greater rates of protein synthesis and deposition and toward much reduced rates of lipogenesis and lipid accumulation in growing swine, sheep, and cattle. Body composition is markedly altered in growing animals administered ST for periods of several weeks or months. The mechanisms of action of ST on tissue growth and metabolism is discussed in detail elsewhere (2–4,71,72).

5.1. Effects on Growth and Composition of Gain. Because ST is a protein, exogenous administration to influence growth must be by subcutaneous or intramuscular injection, or by long-term implant. Ingestion would destroy biological activity, as has been demonstrated in safety trials. Maximal increases of overall mean plasma or serum concentrations to approximately 10- to 13-fold control concentrations are achieved in a dose-dependent manner with daily doses up to 200 μg/kg body weight (BW) in pigs, cattle, or sheep. Elevated concentrations are maintained for approximately 8 to 12 hours after administration, depending on dose.

The dramatic effects of exogenous porcine ST (pST) administration are demonstrated by the results of dose-response studies, using growing pigs treated for 6 to 12 weeks, shown in Table 2. The maximum response is not achieved at the same dose for all response variables (2,73–77). Average daily gain is increased with increasing dose of pST, ie, up to 20% with 150 μg/kg body weight per day; feed conversion efficiency is improved throughout an even greater dose

Table 2. **Effects of Porcine Somatotropin (pST) Dose on Growth Performance**[a]

	pST dose, μg/kg · d[b,c]					
Item	0	50	100	150	200	SEM[d]
number of pigs	10	10	10	10	10	
initial weight, kg	30.8	31.2	31.3	30.7	30.8	0.94
average daily gain, g	890	990	1030	1000	1040	30
daily feed intake, kg	2.86	2.51	2.35	2.20	2.15	0.90
feed:gain ratio	3.23	2.53	2.30	2.20	2.09	0.08
carcass tissue accretion rate, g/d						
protein	93	138	150	152	158	4.0
lipid	264	144	104	59	30	11.0
ash	24	31	34	34	34	1.0
chilled side weight, kg	33.7	34.0	33.4	32.5	32.3	0.41
muscle, kg	15.7	19.6	19.9	20.5	21.4	0.45
adipose, kg	11.6	7.2	5.0	3.8	3.0	0.47
bone, kg	3.7	4.0	4.1	4.2	4.3	0.10
skin, kg	1.8	2.1	2.5	2.5	2.5	0.08

[a]Pigs received daily injections of excipient or the specified dose of recombinant pST. Data are least square means summarized from Refs. 73 and 74.
[b]Kilograms of body weight.
[c]Confidence level >95%.
[d]SEM = standard error of the means.

range. The latter is explained in part by the continued reduction in feed intake with further dose increments. These relationships have been documented by numerous studies in market pigs fed ad libitum. Carcass protein accretion rates are increased up to 74%, coincident with an 82% decrease in lipid accretion rate when pST was administered from 30 to 90 kg body weight (BW). Water accretion rates paralleled protein accretion rates, and ash accretion rates were increased 26–40%. The observed stimulation of bone growth by ST is also dose-dependent. Near maximal response is achieved at pST dose of 100 μg/kg BW. Weight of bone in the carcass increased 10–17%, and skin mass increased 15–38% with increasing pST dose.

Two important aspects of the relationships between growth performance and ST administration are (*1*) the maximum increase in rate of body weight gain may be constrained not only by reduced feed intake, if nutrient density is inadequate, but also by reduction in adipose weight which more than offsets the increase in muscle mass; and (*2*) response in protein accretion to pST doses above 100 μg/kg BW is not parallel in lipid accretion rate. The reduction in lipid accretion rate is linear from 50 to 200 μg/kg BW of pST, suggesting that the physiological effects of ST on composition of gain reflect independent effects on skeletal muscle and adipose tissue. In general, exogenous ST administration does not significantly alter growth or composition in avian species.

Growing ruminants, eg, lambs and cattle, also respond to exogenous ST administration in a dose-dependent manner, but responses are generally of lesser magnitude than those observed in pigs (78,79). It has been unclear if this was

the result of biological differences between species, or whether nutritional constraints of the more complex ruminant digestive system were responsible. Significant effects have, however, been demonstrated in lambs (80–83) and cattle (79,84). Typical responses of growing lambs to daily exogenous ST administration are shown in Table 3 (85). Average daily gain increased 12–19%, and feed conversion efficiency increased 20–22% in lambs. In contrast to the reduction observed in pigs, feed intake has generally not changed with ST treatment in growing lambs. Carcass protein and moisture accretion rates increased 36 and 33%, respectively, and lipid accretion rates were reduced 30%. These relative responses are approximately one-half those observed in growing pigs administered similar doses of ST for similar treatment periods. However, the 18% increase in individual hind leg muscle weights observed in Table 2, and the 24% increase in total dissected muscle observed in ewe lambs treated with ST (86) were not markedly different.

The more variable responses with growing cattle appear to result from lower doses, nutritional constraints, or lesser responsiveness of younger animals, ie, veal calves. A dose-dependent reduction in feed intake in finishing cattle, which also reduced average daily gain, has been observed (84). However, carcass composition was improved in a dose-dependent manner.

Table 3. **Effects of Ovine Somatotropin (oST) and Human Growth Hormone-Releasing Factor (hGRF) on Growth and Composition of Gain in Lambs**[a]

	Treatment				
Response	Control	oST[b]	5 μg hGRF[c]	10 μg hGRF[c]	SEM[d]
number of animals	18	19	20	20	
plasma variables					
oST, ng/mL	2.15	22.3	4.74	5.14	0.92
IGF-I, ng/mL[e]	278.4	469.0[c]	453.2	444.1	27
growth performance, % difference vs control					
average daily gain, g	304	14[c]	13	1.6	12
feed:gain ratio	4.99	−22.4[c]	−18	−19	0.24
composition of carcass gain					
number of animals	9	9	10	10	
protein accretion, g/d	17.2	36	30.8	34.9	1.0
water accretion, g/d	55.6	33.5	19.6	28.8	2.7
lipid accretion, g/d	79.9	−30.4	−21.2	−28.4	3.4
ash accretion, g/d	5.0	18	32[b]	42[b]	0.6
semitendinosus weight, g	91.6	20	10.5	15	2.1
semimembranosus weight, g	261.5	15[c]	10.7	7.6	5.8

[a]Lambs received saline, oST at 40 μg/kg BW, or the indicated dose of hGRF per kg BW four times per day for 42 or 56 days. Half of the lambs were withdrawn from treatment after 42 days. Carcass data shown are for lambs treated 56 days. Carcass composition data were analyzed by analysis of variance using carcass weight as the covariate. Data are summarized in Ref. 85.

[b]Confidence level >99% vs control, unless otherwise noted.

[c]Confidence level >95% vs control, unless otherwise noted.

[d]SEM = standard error of the means.

[e]IGF-I = insulin-like growth factor I.

Age, Gender, and Genotype Interactions. Young pigs, ie, birth to 15-kg live weight; bob veal calves, ie, newborn calves; and young lambs do not consistently exhibit improvement in growth performance or composition of gain in response to exogenous ST administration. This is explained in part by the apparent lack of the full complement of ST receptors in responsive tissues in very young animals. Alternatively, fractional rates of protein synthesis are highest in animals shortly after birth and decline with increasing weight gain. It may be that rates are near maximum in early development of the animal, and further increases may not be possible. Reduction of lipid accretion rate appears to be greatest when ST is administered during the later phases of growth, ie, when animals are approaching normal market weights and beyond (87). This is the stage of growth when lipid accretion rates are still increasing or are maximal in animals fed a high energy diet at ad libitum levels of intake.

Intact males exhibit faster rates of weight gain, more efficient conversion of feed-to-live weight gain, and leanest carcasses among genders of meat animals. However, intact males are not routinely used for pork or beef production in the United States. Exogenous administration of pST can reduce gender differences at moderately high (100 μg/kg) doses (88), although very high (200 μg/kg) doses were required to completely eliminate these differences in one study (73). Conversely, genotype differences in growth performance and composition of gain are not removed when these same dose ranges are used (73,89–92). The relative changes appear to be greatest in inferior genotypes, ie, those having lower protein accretion rates. Direct comparisons of the effects of ST among gender or genotypes of sheep and cattle are few. However, ewe lambs, which exhibit greater rates of lipid accretion than castrated males at the same live weight, exhibit greater reductions in fat accretion and greater responses in growth performance than wether lambs when either ST or growth hormone-releasing factor (GRF) was administered over an eight-week period prior to slaughter (85).

Nutritional Interactions. The large increases in protein deposition in growing animals administered ST may suggest that dietary protein and/or energy intake requirements may be increased. Protein accretion and growth of skeletal muscle may be constrained by inadequate intake of protein or energy. Nutrient requirements vary among growing animals of the same species and age, and protein and energy intake requirements are best defined by titration experiments in which whole-body protein accretion rates are used as the measured response variable (2,93–95). This approach was used to study the effects of ST administration (95–97). Results suggest that amino acid requirements are not changed in young pigs, ie, 20–55-kg live weight, when basal diets are adequate for the untreated pigs. However, amino acid requirements may be increased by a small amount in heavier pigs, ie, 55–110-kg live weight, when porcine ST is administered. The increase in protein accretion rate is accomplished in part by an increase in the percentage of absorbed protein (amino acids) which is deposited or retained. Increased efficiency of protein utilization is observed in both swine and growing ruminants administered ST (72), but the mechanisms by which this is achieved have not been clarified. The gain in lean tissue growth and efficiency of feed conversion achieved with ST or other growth promotants depend on adherence to the fundamental concepts of protein and energy nutrition.

6. Growth Hormone-Releasing Factor

Exogenous administration of the naturally occurring growth hormone-releasing factor (GRF(1-44NH_2)) stimulates ST secretion and increases circulating concentrations of ST in growing pigs, cattle, and sheep (98–100). Maximum elevation of ST concentration is achieved within approximately 5–15 minutes after GRF administration, depending on mode of administration (101). Duration of elevated ST concentration is short, approximately 30–45 minutes, and return to near basal ST concentrations occurs within 60–90 minutes. This is a much shorter duration than the 8–10 hours achieved with direct administration of ST. Therefore, to obtain chronic elevation of ST concentration in the blood, intermittent administration or continuous release, as from an implant of GRF, would be necessary (see CONTROLLED RELEASE TECHNOLOGY, AGRICULTURAL; CONTROLLED RELEASE TECHNOLOGY, PHARMACEUTICAL).

Twice-daily sc injection of 10 or 20 μg human GRF (hGRF)(1-44)NH_2/kg BW for 36 days in barrows weighing 78 kg improved feed conversion efficiency and lean content of the ham (102). However, treatment with hGRF was less effective than pST injection of 20 or 40 μg/kg BW at the same frequency (103).

For growing wether and ewe lambs (85), four daily sc injections of synthetic hGRF at 5 or 10 μg/kg BW for eight weeks is nearly equivalent to injection of oST for improving growth performance and composition of gain (Table 3). Overall mean plasma ST concentration increases 2.5-fold when compared with controls, and lambs do not become refractory to the hGRF after 3, 6, or 8 weeks of administration. Although feed:gain ratios are reduced 18% with both doses of GRF, the higher dose reduces feed intake 6% and impairs an increase in daily gain. Carcass protein accretion rate increases 30–35% coincident with a 21–28% reduction in lipid accretion rate and 32–42% increase in ash accretion rate; the weights of two hind leg muscles show an increase of 10–15%. The overall mean plasma concentration increases to only half that achieved with oST administration, but IGF-I concentrations increase to an equivalent extent. Continuous sc administration of GRF for five weeks is as effective as GRF injection four times per day in significantly altering growth performance and carcass composition in wether lambs.

A shorter synthetic analogue of the native hGRF molecule, ie, hGRF(1-29)NH_2, has been shown to be as potent as native hGRF(1-44) in stimulating ST secretion in several species (104). Because the first 29 amino acids contain the active domain of the molecule for stimulating ST secretion, other even more potent (1-29) analogues have been synthesized and administered to growing pigs. Administration of a superactive analogue, ie, (desamino-Tyr^1, Ala^{15}) hGRF(1-29)NH_2, by sc injection three times daily in pigs from approximately 50 to 105 kg BW increased serum pST in a dose-dependent manner (105). At a dose of 6.66 μg/kg BW, serum ST concentrations were elevated for a significantly longer period of time, over four hours total, than in other studies, which resulted in an approximate threefold elevation in mean ST concentration. Average daily gain was not significantly increased, but feed intake was reduced 15% and feed:gain ratios were reduced 20% using the GRF analogue. Treatment increased skeletal muscle mass 16%, reduced adipose tissue mass 25%, increased bone mass 19%, and increased skin mass approximately 30% (106). These changes were

equivalent in magnitude to those observed using moderate doses of exogenous pST.

Because administration of GRF is presumed to act through the same mechanisms involved in ST mediation of metabolism and tissue growth, similar interactions with gender, genotype, and nutritional status are expected.

7. β-Adrenergic Agonists

Synthetic compounds called β-adrenergic agonists exhibit profound effects on growth and metabolism of skeletal muscle and adipose tissue in growing animals. Phenethanolamines have been categorized as β-adrenergic agonists because of the similar structural and pharmacological properties to the endogenous catecholamines, norepinephrine [51-41-2] (**7**) and epinephrine [51-43-4] (**8**). Among the most extensively studied compounds are clenbuterol [37148-27-9] (**9**), cimaterol [54239-37-1] (**10**), L-644-969 (**11**), ractopamine (**12**), and salbutamol [18559-94-9] (Fig. 2.) Use of ractopamine in finishing pigs was approved by the FDA in December, 1999, under the commercial name of paylean.

The β-adrenergic agonists are all orally active, and most have been shown to repartition nutrient use toward enhanced skeletal muscle growth, or protein deposition, and reduced lipid accretion. However, broad generalizations regarding efficacy and mode of action cannot be uniformly applied because differences exist in responsiveness among mammalian and avian species, and among dose-response relationships (5,6,107,108). For example, clenbuterol, cimaterol, and

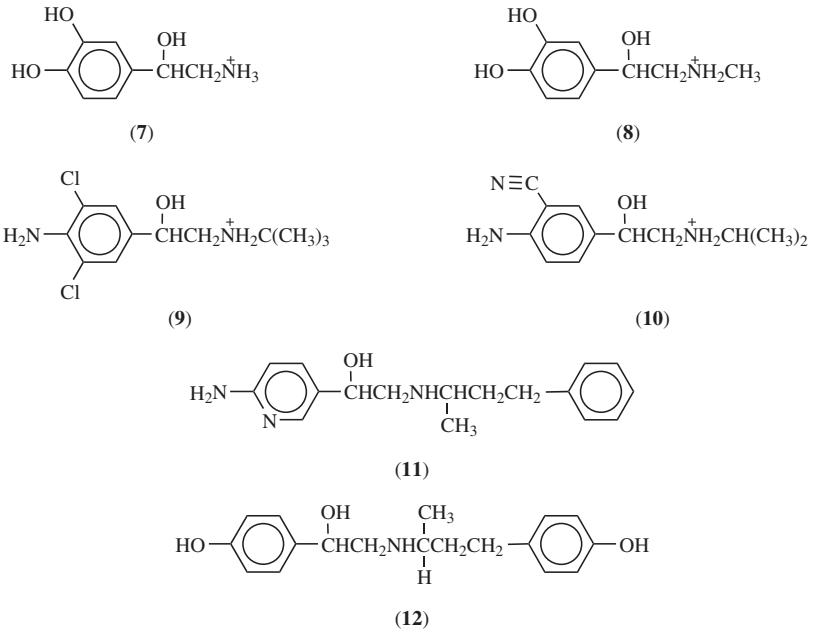

Fig. 2. Chemical structure of the endogenous catecholamines, epinephrine (**8**), and norepinephrine (**7**), and several synthetic phenethanolamines that alter animal growth.

L-644,969 are particularly effective in growing ruminants, ie, lambs and cattle, at doses at 1–10 ppm in the diet, whereas ractopamine is less effective, requiring administration at doses of 20–80 ppm for maximal effect on growth or body composition (7). The basis for these differences is not entirely clear, but may be related to receptor specificity, pharmacokinetics, or development of refractoriness with chronic administration.

7.1. Effects on Growth and Composition of Gain. The β-adrenergic agonists that alter skeletal muscle and adipose tissue growth in animals are orally active, unlike somatotropin, other peptide hormones, or growth factors. These compounds increase skeletal muscle mass and reduce lipid content of most adipose tissue deposits in a dose-dependent manner, with little or no effect on bone. These effects were first observed in rats (109), but have subsequently been described in all domestic farm animal species, ie, lambs, cattle, and pigs, and in poultry, ie, broiler chickens, turkeys, and ducks. Increased rates and efficiency of live weight gain are not consistently observed, and depend on the dose, treatment interval, and overall effect on composition of gain. Efficacy is reduced at extremely high doses (110–112). Largest, but typical, responses include 20–30% increases in average daily gain and 15–20% reductions in feed:gain ratios of lambs fed 1–10 ppm cimaterol, L-644,969, or L-655,871 in conventional mixed concentrate diets offered ad libitum (Table 4) (5). Skeletal muscle mass of

Table 4. **Effects of β-Agonists on Growth and Carcass Composition of Growing Lambs**

		Control values and proportional responses, %				
				Carcass composition, %		
Treatment and dose, ppm	Treatment period, d	ADG,[a] g/d	Feed:gain[b]	Protein	Lipid	Reference
Cimaterol[c]	45					113
0		352[d]	4.94	66.9	16.6	
0.57		3.7	0	6.4	−16.7[d]	
2.29		17.9	−7.3	5.2	−16.3[d]	
11.42		19.3	−14.7[d]	9.0	−33.1[d]	
Cimaterol						114[e]
0	21	170	6.5	15.04	26.7	
10	21	25	−10.0	10.6[d]	−25.0[d]	
0	42	165	6.0	14.3	29.2	
10	42	20	−15.0[d]	19.6[d]	−20.0[d]	
L-655,871	42					115
0		211	7.26	15.11	32.6	
0.25		23.7[f]	−12.2[f]	7.3	2.2	
1		26.1[f]	−15.9[f]	9[d]	0	
4		29.4[f]	−19.9[f]	12.6[d]	−6	

[a]ADG = average daily live weight gain.
[b]Kilograms feed per kg live weight gain.
[c]Data for carcass composition corresponding to protein and lipid are percent-dissected skeletal muscle and adipose, respectively.
[d]Confidence level >95%.
[e]Lambs were housed in metabolism crates.
[f]Confidence level >99%.

individual muscles of the hind leg or total dissectable muscle mass in the carcass is increased 10–30%, and dissected adipose tissue may be decreased 15–30%. Similar responses have been observed in growing cattle, but responses in growing swine are generally smaller. However, when adequate nutriment is provided, similar changes in skeletal muscle and adipose tissue mass have been observed in pigs fed ractopamine (116,117). Responses in poultry are generally similar to or smaller than those observed in swine (118–120).

One striking feature common to all animal responses to these compounds is the lack of anabolic effects on visceral organ or bone growth. Another similarity among responses is that young animals that are nursing, are being reared on milk replacer diets, or have recently been weaned, exhibit little improvement in growth performance or body composition when fed these compounds. Evidence suggests that responses in young animals may be constrained by the lack of complete β-receptor differentiation in responsive tissues. This has not been unequivocally supported. Reductions in lipid accretion rates appear to be highest in animals that exhibit relatively high rates of lipid accretion, ie, those which are more physiologically mature, but are still approaching normal market weights.

The magnitude of the growth performance response is greatest during the early stages of administration, ie, the first few weeks, and in lambs the full effect on relative increases in skeletal muscle mass is achieved within three weeks when relatively high doses are fed (114). Direct infusion of very low doses of cimaterol into the external iliac artery in the hind leg of growing steers results in maximal increases, up to 260%, in amino acid uptake from the circulation at 14 days of administration, but the response is transient and amino acid uptake is returned to normal after 21 days of treatment (121). However, the relative differences in body composition observed in growing ruminants fed β-agonists for three to six weeks are not significantly diminished with continued administration for 10 to 12 weeks. Generalizations across species and the several compounds studied are inappropriate because differential dose-response relationships are apparent. Very few detailed reports that characterize the pharmacokinetics of these compounds in domestic animals have been published (122,123).

7.2. Genotype, Gender, and Nutritional Interactions. There have been relatively few specific gender or genotype interaction studies conducted in growing ruminants fed β-adrenergic agonists. Results available indicate little or no differential effect. Cimaterol and ractopamine increase skeletal muscle growth in both lean and obese swine (124–126), but anabolic responses to ractopamine were larger in genotypes that exhibited superior growth performance and carcass muscle and protein accretion rates (117,127,128). Genotype differences are not eliminated with β-agonist treatment in swine.

Adequate protein and energy intake are prerequisites for achieving maximal response to β-agonist administration. Inadequate protein intake constrains the nitrogen retention response in growing pigs fed 20 ppm ractopamine (129,130), but ractopamine does not increase the efficiency with which growing pigs utilize consumed protein (131). This is in contrast to the observed effect of ST administration. Studies have not been reported for evaluation of effects of β-agonists on the efficiency of protein utilization in growing ruminants. However, additive effects of rumen bypass protein and cimaterol on muscle growth have been demonstrated in lambs (132).

7.3. Mechanism of Action. β-Agonists stimulate skeletal muscle growth by accelerating rates of fiber hypertrophy and protein synthesis, but generally do not alter muscle DNA content in parallel with the increases in protein accretion (133–135). This is in contrast to the effects of anabolic steroids and ST on skeletal muscle growth. Both of the latter stimulate fiber hypertrophy and muscle protein synthesis, but also increase muscle DNA content coincident with increased protein accretion. Whether the β-agonists decrease muscle protein degradation is equivocal.

The short-term or acute effects of the β-agonists may be different from chronic effects. Acute lipolysis and glycogenolysis are not observed beyond the first day or two of treatment. Exact mechanisms of action on lipid metabolism may differ among species. Chronic effects of the β-agonists reduce circulating insulin concentrations; ST treatment causes an opposite change. Whereas residue levels may be of concern with administration of several of the β-agonists, such is not the case for ST or GRF.

8. Health and Safety Factors

The U.S. Food and Drug Administration's Center for Veterinary Medicine thoroughly evaluates the proposed use of any compound, natural or synthetic, used in food-producing animals for human food safety, safety to the animal of intended use, and safety to the environment. A comprehensive review of the FDA approval process for compounds administered to food-producing animals is available (136). When a compound receives approval by the FDA, the efficacy and safety have been extensively investigated, and necessary labeling, handling, use, and withdrawal time requirements, if any, are determined. This information is provided by manufacturers of the compound to the food animal producers, giving appropriate handling, dose, mode of administration, and other use restrictions, guidelines, and procedures. Technical bulletins and reference manuals are available from the manufacturer of each approved product. The Food Safety and Inspection Service (FSIS) of the USDA is responsible for ensuring that USDA-inspected meat and poultry products are safe, wholesome, and free of adulterating residues. The FSIS conducts the National Residue Program (NRP) (137) to help prevent the marketing of animals containing unacceptable (violative) residues from animal drugs, pesticides, or potentially hazardous chemicals. The monitoring and surveillance activities of the NRP provide assurance that meat and poultry products produced from animals slaughtered under federal inspection are in compliance (see MEAT PRODUCTS). Not all animal growth regulators produce residue levels that may require withdrawal of the compound before the animal is marketed, eg, the anabolic steroid implants used in growing cattle. Only MGA carries a withdrawal requirement, ie, 48 hours.

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