Use of Repartitioning Agents to Improve Performance and Body Composition of Meat Animals

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Introduction

Maximizing Livestock Efficiency and the Problem of Animal Obesity

Constraints on land and energy use (Ward, 1980) in association with competition by man himself for the world feed gain supply (Barr, 1981) have necessitated that production efficiency of livestock continue to be improved if it is to remain competitive with other sectors of agriculture engaged in supplying man's food requirements. One strategy of maximizing livestock output that has been used very effectively over the past several decades has been genetic selection for animals demonstrating rapid growth rates. Unfortunately, this selection process has not adequately dealt with the problem of excess fat in cattle, sheep, swine and poultry (Allen et al., 1976). To illustrate the magnitude of the problem, it has been calculated that in the beef industry alone in the United States over 3 to 4 billion pounds of nearly worthless excess fat are trimmed off carcasses each year (Allen et al., 1976). Production of excess fat represents a tremendous waste of resources. Furthermore, increased concern over possible adverse consequences of diets high in saturated fats and cholesterol to human health has led to increased consumer demand for a lean meat product. Thus, a critical issue facing the livestock industry of today is to reduce levels of carcass fat while maximizing lean tissue output.

Current Technology for Improving Carcass Composition

Various methods have been tried to combat this problem of excessive fat deposition. All of these methods suffer from certain disadvantages. Genetic selection for increased carcass leanness in swine, apart from being a long tedious process, has sometimes been associated with an increased incidence of undesirable traits, such as porcine stress syndrome (PSS) or skeletal problems. Manipulation of the dietary regime of an animal has been used successfully to reduce carcass fat. Restrictive feeding regimes, such as are practiced in the European swine industry, result in leaner carcasses but growth rates are impaired (Vanschoubroek et al., 1967). Nutritional factors which have been shown to modulate fat deposition in broilers include dietary fat levels (Deaton et al., 1981), calorie:protein ratios (Edwards, 1980), water:feed ratios (Pesti and Marks, 1983; Marks, 1983), feed restriction (Arafa et al., 1983) and sodium chloride content of the diet (Lightsey et al., 1983). Reducing fat deposition by such methods is again, however, usually associated with adverse effects on bird performance. Various chemical or hormonal treatments have also been used in an effort to reduce carcass fat. Available implants and feed additives used for improving animal performance do not have consistent effects on carcass composition. In some instances, use of estrogenic substances, such as trenbolone acetate, resorcylic acid lactone, estradiol and combinations thereof, has been reported as moderately increasing protein and decreasing fat of ruminants (Galbraith et al., 1980; Coelho et al., 1981; Heitzman et al., 1981; Yasin and Galbraith, 1981; Griffiths, 1982). However, other studies demonstrate no significant improvement in composition associated with increased rate of gain (Thomas and Armitage, 1970; Wilson et al., 1972; Embry and Gates, 1976; Wiggins et al., 1976, 1979; Prior et al., 1978; Rumsey, 1982; Gregory and Ford, 1983; Mathison and Stobbs, 1983). In general, estrogenic or androgenic compounds reduce performance in growing-fattening swine. Although in some cases increased carcass leanness has been reported, drug administration has been associated with abnormal sexual function and behavior (Woehling et al., 1951; Sleeth et al., 1953; Beeson et al., 1955; Perry et al., 1955; Noland and Burris, 1956; Heitman and Clegg, 1957; Thrasher et al., 1959). Daily injections of epinephrine, norepinephrine or nicotine reduce both fat accumulation and performance in swine (Cunningham et al., 1973) but fail to improve carcass composition in broiler chicks (Cunningham, 1963).

Based on the need to produce lean muscular carcasses, there appears to be considerable commercial potential for a chemical agent which could be used (fed or implanted) by animal producers to improve carcass composition without concomitant adverse effects on performance or the need to significantly alter nutritional or management practices.

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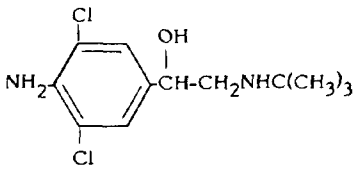
The Discovery of Repartitioning Agents

Dramatic shifts in nutrient partitioning are known to occur with changes in physiological state, such as onset of lactation (Bauman and Currie, 1980) or rapid growth (Bauman et al., 1982). During this process, which has been termed homeorhesis (Bauman and Currie, 1980), nutrients are directed from the gastrointestinal tract and adipose tissue either toward the mammary gland for milk synthesis or towards skeletal muscle for tissue hypertrophy. Thus, it appeared possible to increase lean tissue growth by mimicking this repartitioning process using chemical or hormonal means. The term "repartitioning agent" is used to describe an agent which will direct substrates away from adipose tissue depots and towards muscle accretion.

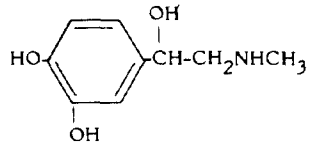
Successful repartitioning should also result in the added bonus of an improvement in animal efficiency (Etherton and Meserole, 1982). The energetic input for protein (not muscle) and fat synthesis is approximately equal (van Es, 1977). However, because muscle contains more water than does fat, a greater quantity of energy is required to produce 1 kg of adipose tissue than is required to produce 1 kg of muscle. Thus, producing (by repartitioning) 1 kg of muscle instead of 1 kg of fat requires less energy or dietary feed input, and should result in improved animal efficiency.

About twelve years ago, Cyanamid initiated a search for repartitioning agents using a rodent model system. Recently, a series of compounds (Baker et al., 1983a; Asato et al., 1984), was discovered which appeared to possess the functional characteristics of a repartitioning agent as described above. Clenbuterol (benzylalcohol, 4-amino-α-(t-butyl-amino) methyl-3,5-dichloro) (Figure 1) is an example of one of these compounds which has been evaluated in rats (Baker et al., 1983a), swine (Ricks et al., 1984a), poultry (Dalrymple et al., 1983; 1984b), sheep (Baker et al., 1983b; 1984) and cattle (Ricks et al., 1983; 1984b) and whose activity appears to translate across species (Dalrymple et al., 1984a).

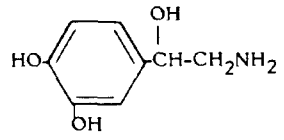
Figure 1



Clenbuterol



Epinephrine



Norepinephrine

Figure 1. Structure of clenbuterol, epinephrine and norepinephrine.

Meat Animal Evaluation of Repartitioning Agents

Ruminants

Some of the most dramatic effects of repartitioning agents in altering body composition are observed in finishing lambs (Baker et al., 1983b; 1984). The results of one study in which clenbuterol was administered in the diet to finishing lambs are shown in Table 1. After eight weeks of treatment with clenbuterol at 2 ppm, gain and feed efficiency were improved 24% and 19%, respectively, above control values. Carcass characteristics were evaluated at sacrifice on animals of constant carcass weight. Longissimus muscle area was increased 41.5%. Various indices of fat deposition indicated that substantial reduction in both subcutaneous and internal fat depots had occurred. USDA quality grade was essentially unchanged by treatment, while yield grade was improved by one grade point. The extent of skeletal muscle hypertrophy with associated reduction in subcutaneous fat is illustrated in Figure 2.

Table 1. Performance and Carcass Characteristics of Wether Lambs Fed Clenbuterol for 8 Weeks

	Clenbuterol level (ppm in feed)	
Observation	*0*	*2*
Average daily gain (kg)	212	263**
Feed/gain	8.31	6.72**
Dressing %	54.6	57.2*
Longissimus area, (cm^2)	16.85	23.85**
Semitendinosis muscle wt, g	143.8	176.9**
Fat depth, 12th rib (mm)	5.9	3.7**
% Kidney and pelvic fat	3.6	2.3**
USDA quality grade (1-12)[1]	9.6	10.1
USDA yield grade (1-5)	3.5	2.5**

[1] 12 = Prime +, 11 = Prime average, 10 = Prime −, 9 = Choice +, etc.
* $p \leq .05$
** $p \leq .01$

Figure 2

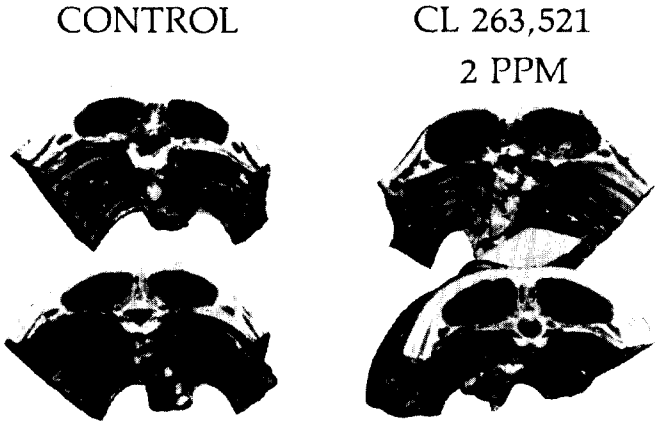


Figure 2. Transverse section through the 12th rib of Lambs fed clenbuterol (CL 263,521).

Similar effects of clenbuterol on carcass characteristics have been shown in one safety study conducted in feedlot cattle (Table 2) (Ricks et al., 1983; 1984b). Clenbuterol at levels of 0, 10 or 500 mg/head/day was administered in the feed to 24 finishing Hereford steers (350 kg) for 98 days. Rib eye area was increased 11% to 16% and yield grade 1 to 1.5 grade points. A 36% to 42% reduction in rib eye fat depth was observed along with a 23% to 33% decrease in kidney, pelvic and heart fat. Interestingly, there were no apparent effects of treatment on marbling, suggesting that subcutaneous and internal fat depots are more readily mobilized by these agents than are intramuscular depots. Composition analysis of the hindquarters verified that an increase in protein and associated water deposition had occurred with a concomitant reduction in fat. Figure 3 shows the muscle hypertrophy that occurred with treatment in the loin muscle and associated reduction in subcutaneous fat. In this study, no improvements in animal performance, as measured by average daily gain and feed efficiency, were noted. However, this may have been due to the drug being administered as a top-dressing.

Table 2. Performance and Carcass Characteristics of Feedlot Steers Fed Clenbuterol for 98 Days

	Clenbuterol level (mg/head/day)		
Observation	*0*	*10*	*500*
Number of animals	8	8	8
Average daily gain (kg)	1.098	1.007	.868*
Feed/gain	11.83	12.04	11.89
Slaughter weight (kg)	447	436	424
Dressing %	63.7	64.5	63.5
Kidney, pelvic and heart fat (%)	2.52	1.93*	1.68*
Longissimus area (cm^2)	79.6	88.1*	92.6**
Fat depth, 12th rib (cm)	1.29	.83**	.75**
Marbling[a]	4.06	3.75	3.63
Yield grade (1-5)	2.7	1.7**	1.2**
Carcass Composition			
Fat %	35.9	28.7**	25.3**
Protein %	15.3	17.3**	17.5**
Water %	47.7	52.4*	55.1**

* $p \leq .05$
** $p \leq .01$
[a] 1 = practically devoid, 9 = abundant

Monogastric Animals

A number of studies have been conducted in finishing swine (Ricks et al., 1984a). Repartitioning effects of clenbuterol in this species are also clearly evident. Table 3 shows the results of one study in which clenbuterol was administered to barrows and gilts from 50 kg until they reached a constant (market) weight of 110 kg. At levels ranging from 0.05 to 1 ppm in the diet, fat depth over the loin was reduced 7% to 12% and back fat thickness reduced 5% to 11%; longissimus area was increased 9% to 21%. Composition analysis on the whole carcass confirmed repartitioning activity. No adverse effects on meat quality were noted. Moreover, there was no indication of thin bellies. Muscle

Figure 3

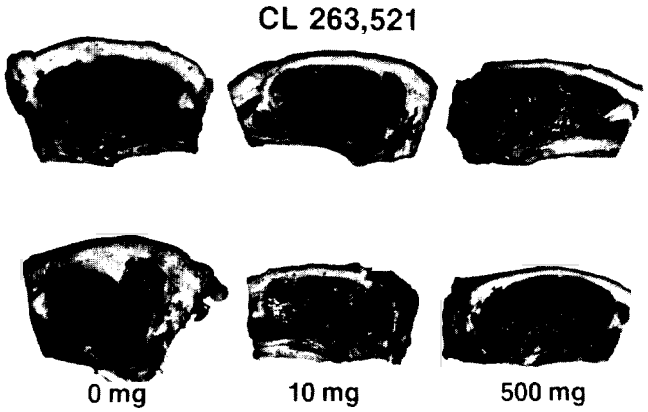


Figure 3. Twelfth rib interface of steers treated with clenbuterol (CL 263,521).

marbling tended to be increased. This observation is in contrast to the effect observed in cattle, in which marbling was not altered. We have no explanation for this apparent difference between species. In our trials, clenbuterol has not consistently improved swine performance. However, recent unpublished data with a related analog has indicated positive performance responses, especially at lower dosage levels.

Dramatic effects of clenbuterol on both performance and carcass composition of finishing broilers have been documented (Dalrymple et al., 1983; 1984b). Table 4 shows the results of feeding clenbuterol at 1 ppm to broilers from 28 to 46 days of age followed by a 3 day drug withdrawal period. Gain and feed efficiency were improved 3.3% and 3.0%, respectively, above control values. These improvements have been observed in about 20 floor pen trials and are consistently associated with an improvement in dressing yield of about 0.8 percentage points or 0.032 lb per 4-lb live bird as well as less abdominal carcass fat. Carcass protein is increased as demonstrated by carcass composition analysis.

Mechanism of Action of Repartitioning Agents

The exact mode-of-action whereby repartitioning agents alter muscle and fat deposition in livestock is unknown. However, these agents are members of a class of compounds called beta agonists. Based on the large body of information available in the literature on the function of beta agonists (Table 5), it is possible to speculate on the possible means whereby these agents improve body composition in livestock.

Beta agonists are synthetic compounds which possess many structural and functional features in common with the natural catecholamine epinephrine (Figure 1). Epinephrine exerts many of its metabolic and physiological effects via interaction with tissue receptors termed alpha and beta receptors. Beta agonists act specifically at beta receptors and exert their action via an increase in intracellular levels of cyclic AMP (Fain and Garcia-Sainz, 1983). Beta receptors can be functionally further subdivided into beta 1 and beta 2 receptor subtypes (Lands et al., 1967). The proportion of beta 1 or 2 receptors found within any tissue or organ within the body is a characteristic of that tissue or organ. For

Table 3. Performance and Carcass Characteristics of Barrows and Gilts Fed Various Levels of Clenbuterol from 50 kg to Market Weight (110 kg)

	Clenbuterol level (ppm in feed)			
Observation	*0*	*.05*	*.1*	*1.0*
Avg. daily gain (g)	765	776	741	717*
Feed/gain	3.21	3.13	3.19	3.42
Dressing %	74.7	74.7	75.1	75.6*
Avg. backfat thickness (cm)	3.59	3.41	3.20**	3.34
Longissimus area (cm^2)	34.7	37.8*	38.5*	42.1**
Fat depth over loin (cm)	3.39	3.14	3.16	2.99*
Belly thickness (cm)	4.86	4.83	4.70	5.00
Muscle marbling (1-5)[a]	1.78	2.04	1.77	2.25*
Muscle color (1-5)[b]	2.80	2.74	2.59	2.65
Muscle firmness (1-3)[c]	1.80	1.87	1.74	1.87
Carcass Composition				
Fat %	32.04	30.01*	29.98*	28.51**
Protein %	15.78	16.16	16.77**	16.66**
Water %	49.45	51.26*	51.33*	52.09**

* $p \leq .05$
** $p \leq .01$
[a] 1 = traces, 5 = abundant
[b] 1 = pale, 5 = dark
[c] 1 = soft/watery, 3 = firm

Table 4. Summary of Performance and Carcass Characteristics of Broilers Fed Clenbuterol from 28 to 46 Days of Age in Three Trials (sexes combined)

	Clenbuterol level (ppm in feed)	
Observation	*0*	*1*
Weight gain, (g) 28-49 days	1156	1194**
Feed/gain, 28-49 days	2.30	2.23**
Carcass yield at 50-51 days[1]	69.91	70.71**
Abdominal Fat Pad[2]	3.76	3.61
Carcass Composition		
Fat %	16.78	15.88*
Protein %	18.83	19.17
Water %	61.83	62.90**

* $p \leq .05$
** $p \leq .01$
[1] Eviscerated weight/live weight × 100 (without abdominal fat pad)
[2] Abdominal fat pad/eviscerated weight × 100

example, lung tissue and uterine tissue have primarily beta 2 receptors. Stimulation of these receptors leads to tissue relaxation (Table 5). Thus, beta 2 agonists, of which clenbuterol is an example, have been found useful in human and veterinary medicine for the treatment of bronchial asthma (Del Bono et al., 1977) and for delay of parturition (Wolfe, 1983). In contrast, heart tissue has predominantly beta 1 receptors. Receptor activation leads to a rapid increase in heart rate. Thus, beta antagonists, such as propranolol, have been found useful in human medicine for the treatment of angina.

The role of anabolic hormones, such as growth hormone or insulin, as mediators in the beta agonist-induced improvement in carcass composition is unclear at this time. Alpha adrenergic agonists and beta blockers, but not beta agonists, elicit growth hormone secretion in most species via adrenergic stimulation at the hypothalamic level (Martin, 1980). Beta adrenergic agonists do stimulate insulin secretion (Ahren and Lundquist, 1981). However, the anabolic effects of these agents are probably not mediated via this mechanism because Deschaies and co-workers (1981), using diabetic rats, have shown that insulin is not necessary for the isoproterenol-induced hypertrophy of the tibialis muscle.

However, there appear to be direct effects of catecholamines and beta agonists on adipose tissue metabolism, which might explain the fat-reducing effects of these agents. Adipose tissue lipolysis is stimulated in most livestock species both *in vitro* and *in vivo* by these agents (Mersmann, 1979) (Table 5). In obese rodents, there is a defect in the beta 1 activation of brown adipose tissue thermogenesis by the catecholamine norepinephrine (Trayhurn and James, 1983) which appears to be related to the increased fat deposition in these animals. Recently, certain beta agonists have begun to be examined as potential human anti-obesity agents. In rats, these compounds dramatically reduce fat deposition with little effect on lean body mass (Massondi et al., 1983). Increased fatty acid mobilization from fat depots coupled with increased thermogenesis may explain how these compounds work. It

Table 5. Metabolic, Physiological and Endocrinological Effects of Catecholamines and Beta Agonists

Effector Organ	*Receptor Type*	*Response*	*Comments*
Lung	β_2	tracheal and bronchial relaxation	used to treat human asthma
Heart	β_1	stimulate heart rate	beta antagonists used in humans to treat heart disorders
Adipose (white)	β_1?	increase lipolysis	receptor type appears to vary with species, effect on lipogenesis unknown
Adipose (brown)	β_1	increase thermogenesis	mediated predominantly via beta$_1$ receptors
skeletal muscle	β_2?	alters protein turnover	via increased synthesis and/or decreased degradation
skeletal muscle	β_2?	alter contraction states	have opposing effects on red and white muscle fiber types
skeletal blood vessels	β_2	dilation	increased blood flow
Liver	β_2	glycogenolysis	blood glucose up
hypothalamus	β_2	decreased growth hormone levels	alpha agonists stimulate growth hormone secretion in most species
pituitary	β	increase growth hormone release	acute effect – epinephrine claimed as physiological GH factor (Perkins et al, 1984)
pancreas	β	increase insulin	acute effect

remains to be elucidated whether there are any direct effects of these agents on inhibition of fatty acid synthesis in adipose tissue depots.

Beta agonists of the repartitioning agent type, however, also clearly alter skeletal muscle metabolism in some manner. Contraction rate of fast muscles is increased by such agents (Bowman and Zaimis, 1958) whereas in slow muscles, these compounds produce a decrease in tension and in the duration of maximum twitches, resulting in reduced tension and degree of fusion of subtetanic contractions (tremorigenic effect). Beta receptor action has been implicated in these processes (Bohmer and Raper, 1976; Holmberg and Waldeck, 1977). The relationship of these processes to skeletal muscle hypertrophy is unclear. As of yet it is not known whether the response of skeletal muscle hypertrophy observed in animals treated with clenbuterol is due to hypertrophy of both fast and slow muscle fiber types. Epinephrine and certain beta agonists have been shown to reduce protein catabolism (Hill and Malamud, 1974; Li and Jefferson, 1977; Tischler, 1981). Recently, Emery and coworkers (1984) have demonstrated that chronic treatment of rats with clenbuterol will result in enhanced protein synthesis (fractional rate) measured in vivo. It seems probable, therefore, that beta agonists of the repartitioning agent series function by switching on skeletal muscle hypertrophy, probably by a decrease in protein catabolism and/or an increase in protein synthesis. In order that the necessary supply of both energy and substrate components be furnished to the hypertrophying muscle, nutrients are diverted away from adipose tissue and towards muscle. This process is depicted diagramatically in Figure 4.

Impact of Repartitioning Agents on the Livestock Industry

The discovery of repartitioning agents which exhibit such remarkable effects on carcass composition demonstrates that an increase in lean tissue output and associated reduction in carcass fat can be achieved without reducing animal performance. Such agents have tremendous potential for improving the efficiency of livestock production in the future.

Figure 4

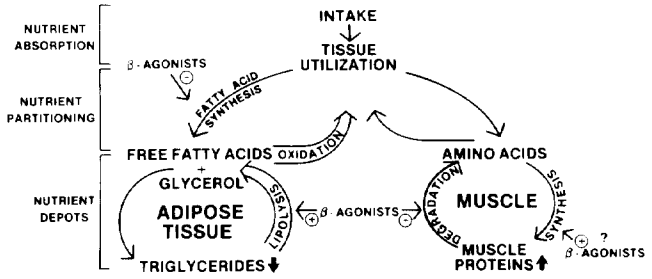


Figure 4. Proposed mode-of-action of Beta-agonists in altering muscle and fat deposition.

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