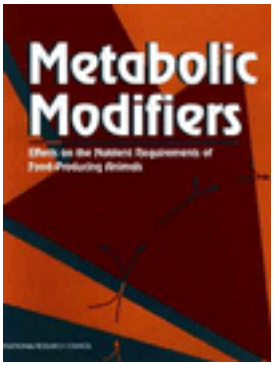

Metabolic Modifiers: Effects on the Nutrient Requirements of Food-Producing Animals

Subcommittee on Effects of Metabolic Modifiers on the Nutrient Requirements of Food-Producing Animals, National Research Council

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Metabolic Modifiers

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Subcommittee on Effects of Metabolic Modifiers on the Nutrient Requirements of Food-Producing Animals
Committee on Animal Nutrition
Board on Agriculture
National Research Council

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Preface

Animal scientists have long sought economical ways to improve the productivity of commercially important domestic animals, to enhance their productive efficiency, and, in the case of meat animals, increase muscle mass and concurrently decrease carcass fat. Remarkable scientific advances during the past 10 years have led to the discovery of two new technologies that achieve these goals—the administration of (1) recombinantly derived somatotropin (ST) (growth hormone) and (2) β-adrenergic agonists (synthetic catecholamine-like analogs). Administration of ST to cows increases both milk production and productive efficiency (milk/unit feed). In meat animals, administration of ST or β-adrenergic agonists improves productive efficiency and carcass leanness. Administration of anabolic steroids enhances growth performance in sheep and beef cattle.

In 1989, under the auspices of the Board on Agriculture's Committee on Animal Nutrition, the Subcommittee on Metabolic Modifiers was appointed to summarize our present understanding of the mechanisms by which ST and β-adrenergic agonists act and to determine, where possible, what effects administration of these metabolic modifiers have on nutrient requirements of domestic livestock.

In this report, we have discussed the current understanding of the mechanisms by which metabolic modifiers alter nutrient partitioning and productive efficiency and what is known about their effects on the nutrient requirements of food-producing animals. In Chapter 1, the subcommittee underscores the role agricultural scientists play to provide optimal nutrition and productive efficiency for food-producing animals to meet the changing needs of consumers and the increasing demands of a growing world population. Chapter 2 addresses our growing knowledge of biology, chemistry, and mechanisms of action of metabolic modifiers that make it possible to alter carcass composition, improve feed efficiency, and enhance growth rate in poultry, sheep, pigs, and cattle, and increase milk yield in dairy cattle. Chapter 3 examines the nutrient requirements and production responses of dairy cattle supplemented with bovine ST (bST) with respect to the yield and composition of milk in relation to breed and genotype, parity, management, environment, and feed intake. Chapter 4 addresses nutritional implications in swine, including constraints to lean growth, and nutrient requirements with respect to intake, digestion, maintenance, and efficiency of nutrient use. Discussion includes estimates of amino acid, mineral, and vitamin requirements in growing swine. In Chapter 5, strategies for administering metabolic modifiers to poultry are discussed, including exogenous ST administration and in ovo manipulations. Nutrient intake recommendations are given along with modeling approaches and empirical predictions. Chapter 6 discusses the effects of metabolic modifiers on growing cattle and growing lambs.

In summary, the subcommittee believes that the full spectrum of advantages available from these technologies can only be realized by increasing our understanding of the effects these metabolic modifiers have and the biological mechanisms and nutritional requirements that account for the changes in performance and productive efficiency.

TERRY D. ETHERTON, *Chair*

Subcommittee on Effects of Metabolic Modifiers on the Nutrient Requirements of Food-Producing Animals

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Executive Summary

Historically, humankind has been confronted with the need to increase food production to meet the growing demands imposed by the expanding world population. And, as societies become more economically developed, per capita demand also increases. The ability to increase world food production has been the result of remarkable scientific advances that increase not only production but also the productive efficiency of agriculture. During the last decade, several new technologies have emerged that increase the efficiency of livestock production as well as meat and milk production to an extent not envisioned 10 years ago. The emerging technologies that are the focus of this report are somatotropin (ST) and β-adrenergic agonists. Because of the extent to which these metabolic modifiers improve productive efficiency (body weight gain or milk yield per unit of feed consumed), improve carcass composition (ratio of muscle:fat) in growing animals, and increase milk yield, it is important to establish whether dietary nutrient requirements are altered and, if so, how diet formulation and nutrient intake might need modification to achieve the maximum beneficial response.

Although metabolic modifiers exert their effects on animal performance in a dose-related manner, it is important to appreciate that nutrient requirements are dynamically affected by many other factors (such as gender, age, weight, and feed management system). Thus, the task of the subcommittee was to review the available literature and, where possible, determine the extent to which treatment with metabolic modifiers affected dietary nutrient requirements of dairy cattle, growing ruminants, poultry, and swine.

DAIRY CATTLE

The subcommittee concluded that current feeding recommendations can be used for cows treated with bovine somatotropin (bST). Milk composition, diet digestibility, maintenance requirements, and the partial energetic efficiency of lactation are not affected by bST. Numerous metabolic adaptations result from bST administration with a consequent increase in nutrient availability for milk synthesis. Depending on nutritional status, nutrients derived from body reserves can provide support for the increase in milk synthesis; but, subsequently, feed intake increases, which provides the nutrients necessary to sustain the increase in milk yield.

Cows treated with bST need to be fed and managed like other cows at similar levels of milk production. When ration density is increased by feeding grain, alteration of ruminal hydrogen-ion imbalance should be managed by the addition of buffers like sodium bicarbonate. Rations should be balanced for rumen degradable and nondegradable protein and ration adjustments with respect to nutrient density should be made on the basis of body weight and condition.

GROWING RUMINANTS

There is some evidence to suggest that amino acid availability at the site of absorption may limit the response of the growing ruminant to metabolic modifiers. Results from studies in which protein was infused abomasally in cattle and lambs and in which sheep were fed fishmeal have demonstrated a marked increase in the growth response (nitrogen retention) to exogenous ST. This suggests that amino acid availability may limit the response to exogenous ST. The subcommittee did not make any recommendations regarding whether β-adrenergic agonists or ST affected nutrient requirements of growing cattle and sheep because few systematic studies have been reported that examined the effects of metabolic modifiers on protein and energy metabolism.

The subcommittee concluded that advances must be made in formulating diets that deliver the appropriate profile and quantity of amino acids postruminally to match the tissue requirement for nutrients when metabolic modifiers are administered

(and alter tissue requirements). This will require adjustments in experimental design to quantify accretion rates of body protein and lipid as a function of dietary inputs.

SWINE

In contrast to other livestock species, swine are quite responsive to the anabolic effects of porcine ST (pST). Considerable information exists in the literature about the effects of pST on nutrient requirements. The available information suggests that protein deposition in the pig is constrained by dietary energy intake. Furthermore, with optimal energy nutriture, lysine, as the first limiting amino acid for growth, will require fortification compared to conventional diet formulations. The subcommittee recommends the adoption of feeding standards formulated on the basis of target tissue growth and composition. This requires adoption of the "ideal" protein concept to diet formulation or some modification of this concept. In this way, significant improvement in the realization of lean tissue growth potential can be achieved. Diet modifications associated with the use of metabolic modifiers can then be logically calculated on a biological basis.

At the present time the subcommittee does not believe it appropriate to recommend a generalized increase in dietary protein intake in conjunction with the use of metabolic modifiers. Rather the use of feeding standards that reference rate and composition of gain of desired tissue (i.e., ideal protein concept) would improve productive efficiency of animals treated with metabolic modifiers, in addition to those not so treated. There is some evidence which suggests that pST improves the efficiency of dietary protein (amino acid) utilization for tissue growth; however, the extent of this improvement and the underlying mechanisms remain obscure. The subcommittee, however, emphasizes that there is a need for additional research to determine the effects of metabolic modifiers on dietary protein (amino acid) utilization and requirements.

POULTRY

Studies conducted with metabolic modifiers have not convincingly shown that they have a positive effect on growth performance in poultry. It is of concern whether using diets formulated using contemporary National Research Council (NRC) recommendations will be adequate to support enhanced growth or to permit efficacy testing of the metabolic modifiers. Diets fortified in amino acids, macronutrients, and enriched in energy content may be required to demonstrate growth enhancement of lean tissue. For research and development purposes, the subcommittee recommends adoption of a standardized diet that does not limit the biological response of poultry to metabolic modifiers.

SUMMARY

New technologies targeted to improve production and productive efficiency of domestic livestock have the potential to markedly benefit animal production. These technologies, depending on the target species, may modify contemporary strategies used for diet formulation. These technologies will, however, amplify inadequacies in either diet design or animal management practices.

The subcommittee identified a need for additional research to determine the appropriate profile and quantity of amino acids that must be available postruminally to match the tissue requirements for nutrients when metabolic modifiers are administered to growing ruminants. The subcommittee believes that additional research is needed to determine the effects of metabolic modifiers on dietary protein utilization and requirements in swine. The subcommittee concluded that new feeding standards formulated on the basis of target tissue growth rate and composition must be adopted. This will require the incorporation of the "ideal protein" concept or some modification of this concept to diet formulation.

The subcommittee has pointed out the need for additional information in a variety of areas. As such, this report is constrained in some respects because of the limited scientific information available. It is our belief that this report will stimulate research to expand our knowledge base about the effects that metabolic modifiers have on nutrient requirements of domestic livestock. This will be essential in order for the advantages of the technology to be fully realized in practice.

1

Introduction

It has become increasingly evident that technological developments in a variety of scientific and engineering disciplines will be needed to support the growing world population, which is expected to double in the next 40 years. Thus, the supply of food required to adequately meet human nutritional needs over the next 40 years is quantitatively equal to the amount of food previously produced throughout the entire history of humankind (Bauman, 1992). The need for technological innovations in agriculture production systems is obvious. The success of agriculture scientists in developing new technologies to enhance food production is perhaps best exemplified by the 45 percent annual return on investment in agriculture research in the United States (Fox et al., 1987).

Food products from animals have always been a mainstay of the American diet, and between 33 and 100 percent of the major dietary nutrients are derived from animal products (National Research Council, 1988a). For example, animal products account for 69 percent of the dietary protein intake. To meet the challenge of world food needs, animal scientists must develop new technologies to increase productive efficiency (i.e., yield of milk/feed input; yield of muscle/feed input), produce leaner animals, and provide increased economic return on investment to the producer.

Technologies that lower the quantity of feed consumed per unit of output (such as meat or milk) will be of benefit to both the producer and consumer because feed constitutes a major component (about 70 percent) of farm expenditures. These technologies also represent an advantage in reducing environmental pollution (National Research Council, 1989; Bauman, 1992; Johnson et al., 1991). A reduction of the quantity of feed required to produce a unit of meat or milk would be expected to reduce fertilizer and other inputs associated with growing, harvesting, processing, and storing animal feed. Likewise, reduction in animal excreta, including methane production (predominantly from ruminants), occurs when productive efficiency is increased.

There is also a real need to reduce fat content of both meat and dairy products. Consumers are concerned about the saturated fat content of animal products because of numerous studies that show saturated fatty acid intake is a major risk factor for coronary disease (Kris-Etherton et al., 1988). Because animal products provide approximately 60 percent of the total saturated fatty acids consumed in the United States (National Research Council, 1988a), it is prudent and timely that new technologies be developed that are more cost effective and efficient in reducing carcass fat than the current practice of trimming the excess fat.

Recent developments have identified several new technologies that will improve the nutritional attributes of animal products and increase productive efficiency (U.S. Congress, Office of Technology Assessment, 1992; Bauman, 1992; Etherton, 1992). Foremost of these new technologies is a group of compounds that modify animal metabolism, referred to as "metabolic modifiers." Metabolic modifiers covered in this report include somatotropin (ST), growth hormone-releasing factor, and β-agonists. All of these metabolic modifiers affect how animals use absorbed nutrients. This is illustrated by considering ST.

Administration of porcine ST (pST) to growing pigs results in more nutrients being directed to lean tissue growth (protein) and less to fat accretion in adipose tissue (Figures 1-1 and 1-2). This shift in nutrient partitioning results in a substantial improvement in feed efficiency, and the quantity of feed per unit of gain can be reduced by up to 35 percent when pST is used (see Chapter 2). Treatment of dairy cows with bovine ST (bST) causes more nutrients to be directed for milk synthesis. Dairy cows are typically managed so that excessive fattening does not occur. In this case, bST treatment has no effect on body composition or milk composition, but milk yield is increased (see Chapter 3). Thus, the proportion of nutrients used for maintenance decreases resulting in a marked improvement in the amount of milk produced per unit of feed consumed (Figure 1-3).

The improvement in carcass quality of growing animals and the increases in efficiency of growth and lactation that occur with the use of metabolic modifiers are unprecedented. For a successful animal production enterprise, however, sound management practices must be followed. This requirement does not change when metabolic modifiers are used. Indeed, there are several studies in which no response was observed with ST treatment of growing pigs or lactating cows because of limitations in the management program. One aspect of the management program that is critically important for successful implementation of these new technologies is nutrition. The primary objective of this report is to discuss the impact of metabolic modifiers on the nutrient requirements of food-producing animals. These effects differ somewhat between growing and lactating animals. In the former, the use of metabolic modifiers results in a major shift in the type of growth (fat versus lean tissue), thereby requiring matching changes in dietary formulations. In contrast, use of metabolic modifiers for lactating dairy cows does not alter the specific nutrient requirements per unit of milk because the composition of milk is not affected. To fully understand and appreciate the effects that metabolic modifiers have on nutrient requirements, it is necessary to consider the biology of their action. Thus, a second objective of this report is to discuss the current understanding of the mechanisms by which these metabolic modifiers alter nutrient partitioning and productive efficiency.

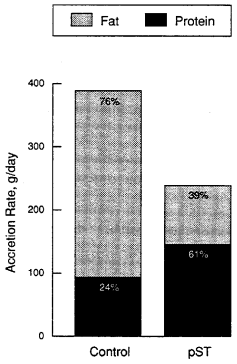

FIGURE 1-1
Accretion rates for protein and fat in pigs over the body weight range from 45 kg to 100 kg (market weight). Adapted from Boyd and Bauman (1989) where daily dose of pST was 120 µg/kg body weight.

FIGURE 1-2
Effects of a maximally effective dose of pST (rpGH) on nutrient partitioning in growing pigs. Pork loins are from pigs treated for 77 days with either excipient (control) or a daily dose of 140 µg pST/kg body weight (Evock et al., 1988). Loin-eye area of the loin from the control pig is 27.2 cm^2; from the treated pig, 51.7 cm^2.

The extensive research conducted with metabolic modifiers have demonstrated that these technologies when appropriately used are effective in improving food animal production and are safe for the target animal and consumer. Following a protracted and thorough review of the use of bovine somatotropin in dairy production, the Food and Drug Administration approved bST for commercial use in the United States in November 1993 (waiting for exact citation). Evidence that supports this approval action can be found in several sources (U.S. Congress, Office of Technology Assessment, 1991; Bauman, 1992; Executive Branch of the Federal Government, 1994). Likewise, extensive research has shown that the other metabolic modifiers under commercial development are safe (reviewed in Etherton, 1991; Etherton et al., 1993).

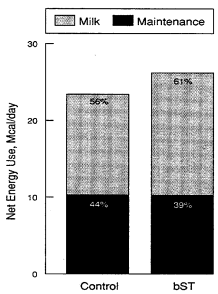

FIGURE 1-3
The effect of bST on the quantity of energy used for milk production and maintenance in lactating cows (from Bauman, 1987).

2

Mechanisms of Action of Metabolic Modifiers

During the past 10 years extraordinary progress has been made in understanding the mechanisms of action of the metabolic modifiers under discussion. This chapter discusses the biology, structure, mechanisms of action, and treatment effects of somatotropin (ST), *β*-adrenergic agonists, and anabolic steroids.

SOMATOTROPIN

It is important to appreciate the benefits that have been realized from research in animal agriculture. With respect to ST, the expansion of our knowledge base has enabled scientists to conceptualize and develop strategies to (1) modify carcass composition, (2) improve feed efficiency, and (3) enhance growth rate and milk yield. This exciting new era in animal agriculture offers unprecedented potential and, in large part, depends on our understanding of the basic biological processes that regulate growth and lactation. It is also important to emphasize that further progress in our understanding of these processes should lead to additional increases in both production performance and productive efficiency.

Downs (1930) and Bierring and Nielsen (1932) were the first to show that an alkaline extract of the anterior pituitary gland reduced carcass fat in rats. This was verified by Lee and Schaffer (1934) who reported that pair-fed rats injected with a crude alkaline extract of bovine pituitaries not only gained more weight, but also contained proportionally more muscle and less fat. Their paper introduced the concept that the "growth hormone" of the anterior pituitary gland could affect the quantity of fat in animals. It was not until 1945, however, that growth hormone was isolated from the anterior pituitary (Li et al., 1945). This allowed Li et al. (1948) to conduct the first experiment to show that crude preparations of ST would reduce carcass fat in rats. Rats were treated 6 days/week for 437 days with a graded injection regimen increasing from 0.4 mg/day to 2.0 mg/day. Carcass fat was reduced by 47 percent.

Results of early studies showing that preparations of ST could decrease carcass fat of rats prompted a number of studies to evaluate the effects of pituitary preparations of porcine ST (pST) on growth and carcass composition of pigs (Giles, 1942; Turman and Andrews, 1955; Henricson and Ullberg, 1960). These studies were inconclusive, probably because the ST preparations were not pure. In 1972, Machlin established that treating pigs with pituitary-derived pST significantly improved weight gain and feed efficiency (Machlin, 1972).

The impact of ST on lactation was also recognized during this same interval. Early studies indicated that administration of anterior pituitary extract affected lactation in laboratory animals (Stricker and Grueter, 1928) and increased milk yield of lactating goats (Asdell, 1932). In 1937, Asimov and Krouze conducted the first substantial study involving more than 500 dairy cows and demonstrated that injections of crude pituitary extract increased milk yield (Asimov and Krouze, 1937). During the 1940s, further research established that the component in the crude pituitary extracts that increased milk yield and stimulated growth was the same molecule, ST (Li et al., 1945; Young, 1947). The first study of the effects of long-term administration of bovine ST (bST) on lactation was conducted by Brumby and Hancock (1955). Milk production was increased approximately 50 percent when twin cows received daily injections of bST for 12 weeks. Similar results were obtained in a subsequent study by Machlin (1973) using a more highly purified source of bST.

Prior to the 1980s, studies with ST were limited in domestic livestock. There was little interest in commercial application for two reasons. First, there was no means for producing large quantities of ST, thus, the supply was limited to that extracted, with varying purity, from the pituitary glands of slaughtered animals. Second, the mechanism of action for ST was thought to involve an acute stimulation in the use of body fat reserves. Accordingly, scientists believed it would be effective only in fat dairy cows with a low milk

yield or in growing animals at the end of the finishing period when fat stores are extensive. Advances in biotechnology made it possible to produce large quantities of ST by recombinant DNA technology. This made it feasible to conduct more extensive investigations which demonstrated that the previously proposed mechanisms were wrong. More recent studies have conclusively demonstrated that chronic administration of recombinant ST results in unprecedented increases in milk production and productive efficiency of dairy cows. It also dramatically improves growth rate, carcass composition, and productive efficiency of pigs.

Structure of Somatotropin

Somatotropin is a protein synthesized in and secreted from the anterior pituitary gland. Secretion of ST is regulated by two peptides that act to either stimulate [growth hormone-releasing factor (GRF)] or inhibit (somatostatin) release of ST from the pituitary gland. Somatotropins from domestic livestock contain 191 amino acids and share a high degree of sequence identity (see Figure 2-1). There are 18 positions that differ between the amino acid sequences pST and bST, but only 2 residues differ between ovine ST and bST. Sequence differences between chicken ST (cST) and ST from other species (Figure 2-1) are much greater (e.g., cST has 77 percent sequence identity to bST). Variants of ST are also produced by the pituitary gland. For example, in the bovine there are four major variants (Bauman and Vernon, 1993).

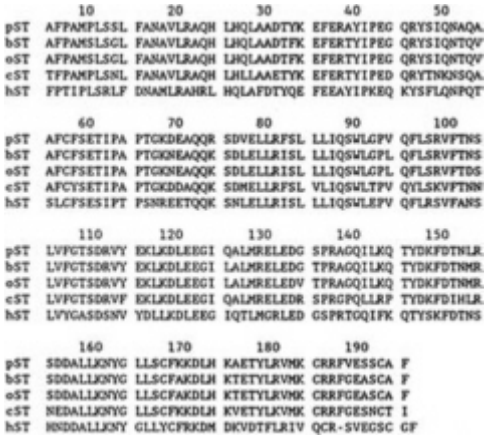

FIGURE 2-1
Comparison of amino acid sequences for somatotropin from different species. pST, porcine somatotropin; bST, bovine somatotropin; oST, ovine somatotropin; cST, chicken somatotropin; hST, human somatotropin; A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; Y, Tyr; V, Val; W, Trp. Amino acid sequences were from the following: cST (Souza et al., 1984); pST (Seeburg et al., 1983); bST, hST, and oST (Miller and Eberhardt, 1983; Nicoll et al., 1986).

It has been known for almost 40 years that pituitary preparations of ST from farm animals and other nonprimates are not biologically active in humans (Bennet et al., 1950; Froesch et al., 1957; Raben, 1959; Juskevich and Guyer, 1990). Subsequent research established that this is because there are considerable differences between the amino acid sequences of human ST (hST) and bST or pST (Wallis, 1975, 1989). Because of these differences, bST and pST are unable to effectively bind to the ST receptor on human cells and initiate a biological response (Carr and Friesen, 1976; Lesniak et al., 1977; Moore et al., 1985; Hocquette et al., 1989).

Effects of Somatotropin

Growth Performance

Numerous studies have been conducted to investigate the effects of different doses of pST on growth performance of pigs. Furthermore, we have a reasonable understanding of the effects pST has on amino acid requirements. Unfortunately, there is less information available on the effects of ST on growth performance of beef cattle, sheep, and chickens, which limits discussion of the effects of ST on nutrient requirements in these species.

Pigs The effects of pST on growth performance have been widely documented. Responses to different doses of pST are summarized in Table 2-1. Magnitude of response in these studies has varied primarily because of experimental design differences including initial body weight, length of study, breed, sex, dose of pST, and diet composition. Despite these differences, however, it is evident that maximally effective doses of pST can increase average daily gain (ADG) by as much as 10 to 20 percent, improve feed efficiency 15 to 30 percent, decrease adipose tissue mass and lipid accretion rates approximately 70 percent, and concurrently increase protein deposition 50 percent. These changes in performance are associated with a decrease in feed intake of approximately 10 to 15 percent.

Some studies have examined the relationship of pST dose to production response (Boyd et al., 1988; Evock et al., 1988; McLaren et al., 1990). These studies have established that the relationship varies considerably among the various parameters that define growth performance (Figure 2-2). For instance, ADG and rates of protein and ash accretion are maximally stimulated at a daily pST dose of about 100 μ/kg BW. In contrast, lipid accretion rate and feed: gain ratio decrease in a more linear manner across a range of pST doses up to 200 μg/kg BW (see Figure 2-2). The difference in the shape of the dose-response curves not only implies that pST affects growth and metabolism of these tissues by mechanisms

that differ but also has important implications from a nutritional perspective. The marked change in compositional growth and growth rate indicate that changes in the dietary nutrient-calorie relationship must be made to support rates of protein deposition observed for a specific dose of pST. As is detailed in Chapter 5, this becomes particularly important in view of the decrease in feed intake of pST-treated pigs.

TABLE 2-1 Effects of Porcine Somatotropin (pST) on Pig Response

pST Dose (µg/kg/day)	Average Daily Gain (%)	Feed: Gain (%)	Carcass Fat[a] (%)	Carcass Protein[b] (%)	Reference
22	10	-4	NR	6	Chung et al., 1985
30	10	-19	-18	36	Etherton et al., 1986
70	14	-17	-25	19	Etherton et al., 1987b
100	16	-24	-32	37	Campbell et al., 1988
140	19	-25	-68	28	Evock et al., 1988
100	16	-32	-51	62	Campbell et al., 1989a
100	36	-28	-63	46	Campbell et al., 1989b
70	18	-22	—	—	Bryan et al., 1989

NOTE: NR, no response;—, not evaluated.

[a] Response represents a composite of percent of carcass fat, kilograms of adipose tissue, or lipid accretion rates.

[b] Response represents a composite of percent of carcass protein, kilograms of muscle, or protein accretion rates.

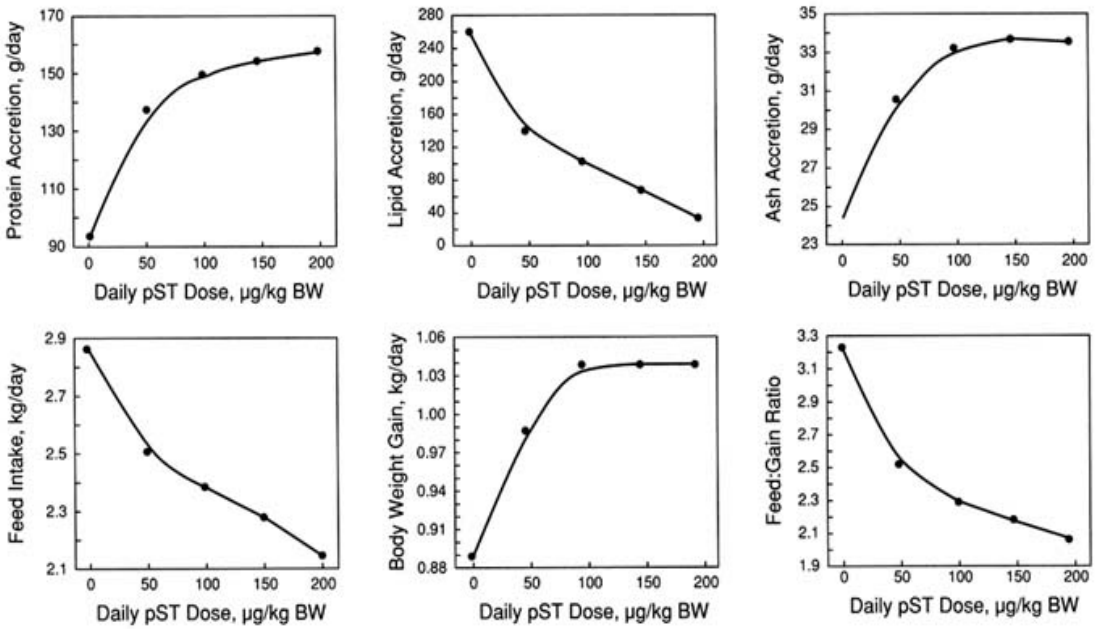

FIGURE 2-2
The dose-response relationship between pST and different parameters of pig growth performance.
BW, body weight. The data were summarized from studies reported by Krick et al. (1992).

Somatotropin must be administered by injection because it is not orally active. In studies reported to date, pST has been injected daily, an approach with limited feasibility for treating a large number of pigs. Thus, for the product to be commercially accepted, it is likely that prolonged-release formulations will need to be developed. A few recent abstracts have described the effects of sustained-release

formulations of pST (Knight et al., 1988, 1989; Klindt et al., 1992), and this is an area of active investigation.

Ruminants Studies examining the effect of ST on growth performance of sheep and cattle have been less extensive than those with pigs. Enright (1989) compiled the results of studies in which cattle and sheep were treated with ST. In general, it appears that the ST dose/growth performance response relationships are similar to those observed with pigs but the magnitude of the responses, in particular the effects on rates of protein and lipid accretion, are substantially less. Possible explanations for these differences are discussed in Chapter 4.

Chickens The effects of cST on chicken growth performance are equivocal (see Table 2-2 and Chapter 6) and differ from those observed for other domestic animals. In some studies, administration of cST increases adipose tissue accretion (Leung et al., 1986; Cogburn et al., 1989a), a response that is the opposite of results for growing pigs and cattle. In addition, some studies have shown that cST decreases protein deposition. The most encouraging results are from Vasilatos-Younken and colleagues (1988) in which episodic administration of cST to older birds markedly improved growth performance whereas continuous infusion had no effect. These authors suggested that the pattern of cST administration is important to attain a stimulatory effect.

TABLE 2-2 Effects of Chicken Somatotropin (cST) on Chicken Response

cST Dose (µg)	Average Daily Gain (%)	Feed: Gain (%)	Carcass Fat[a] (%)	Carcass Protein[b] (%)	Reference
50	7	NR[c]	8	NR	Leung et al., 1986
500 per kg, 3 × per day	4	4	5	NR	Burke et al., 1987
100 per day	NR	—	—	—	Bowen et al., 1987
150 per kg	21	-34[c]	-33	NR	Vasilatos-Younken et al., 1988
200 per kg per day	NR	NR	17	-3	Cogburn et al., 1989a

NOTE: NR, no response;—, not tested.

[a] A response represents a composite of percent of carcass fat, grams adipose tissue, or lipid accretion rates.

[b] A response represents a composite of percent of carcass protein, grams muscle, or protein accretion rates.

[c] Data were presented as body weight gain: feed consumed in this study.

TABLE 2-3 Increase in Milk Yield (kg milk/day above controls) in Response to Bovine Somatotropin (bST)

	bST (mg/day)				
Controls	5	10-15	20-27	31-50	Reference
24.9	+3.6	+3.8	+5.0	+5.7	Chalupa and Galligan, 1989[a]
26.0	+2.8	+4.1	+5.3	+6.2	Chilliard, 1988[b]

[a] Summarized from 7 studies.

[b] Summarized from 20 studies.

Lactation

The effects of bST on milk yield have been documented and discussed in several hundred studies (see reviews by Peel and Bauman, 1987; Chilliard, 1988; Chalupa and Galligan, 1989; Bauman, 1992). Administration of bST following peak milk production (approximately 60 days postpartum) results in a substantial increase in milk yield, and a marked improvement in the persistency of lactation is generally observed. Results from 27 lactation studies are summarized in Table 2-3. Milk yield increases in a dose-dependent manner and the composition of milk is unaltered. Increases of 4 to 6 kg/day have been most frequently observed in long-term studies. In addition, responses have been observed for all dairy breeds examined and in animals of different parity and genetic potential (see Chapter 3).

Summary of Effects of Somatotropin on Growth and Lactation

Studies show that ST markedly increases growth performance in pigs and ruminants and enhances milk production in dairy cows. Overall, this results in an impressive improvement in productive efficiency. The effects of ST on chicken growth performance are equivocal at the present time. It should be emphasized that ST is not magic and the greatest

factor affecting the magnitude of response is quality of management (Bauman et al., 1989b). One management factor of particular importance is the nutritional program. Indeed, there are several studies with growing pigs and lactating cows in which the diet was inadequate in amount and/or nutrient balance, and these investigations observed a negligible response to ST.

Mechanisms of Somatotropin Action

In order to cause such dramatic biological effects on growth performance and lactation, it is evident that ST orchestrates many diverse physiological processes to enable more nutrients to be used for lean tissue accretion (during growth) or milk synthesis (during lactation). Research conducted during the past 10 years has indeed established the diversity of physiological effects of ST (see Table 2-4).

ST affects numerous target tissues in ways that are highly coordinated to effect marked changes in nutrient partitioning among these tissues. The biological effects of ST can be broadly classified as either somatogenic or metabolic. The somatogenic effects are those in which ST stimulates cell proliferation. These effects are thought to be mediated by insulin-like growth factor I (IGF-I) (Rechler, 1988). IGF-I is a potent mitogen that shares some sequence similarities with insulin. In contrast, many of the metabolic effects are a direct action of ST. These involve a variety of tissues, and affect the metabolism of all nutrient classes—carbohydrate, lipid, protein, and minerals (see Table 2-4). As a result the coordinated changes in tissue metabolism alter nutrient partitioning and thus play a key role in increasing growth performance or milk yield.

The principal effect of ST is on partitioning of absorbed nutrients. In lactating cows or growing cattle treated with bST, digestibilities of dry matter, carbon, nitrogen, and energy are not altered (Bauman et al., 1989a; Boyd and Bauman, 1989; Chalupa and Galligan, 1989). The energy expenditure for maintenance or the partial efficiency of milk synthesis is not altered in dairy cows treated with bST (Tyrrell et al., 1988; Sechen et al., 1989a; Kirchgessner et al., 1991a). Likewise, studies with growing pigs and cattle have shown that the energetic efficiency of specific processes is not altered. However, maintenance costs are increased by pST administration in pigs, which is consistent with the fact that pST-treated animals have a greater proportion of lean tissue at a given body weight. Verstegen et al. (1989) reported that the maintenance requirement (ME_m) increased about 10 percent; Campbell et al. (1988) found that maintenance requirement increased about 17 percent.

The biological effects of ST are initiated by binding to the ST receptor on the target cell. The ST receptor has been cloned for humans (Leung et al., 1987), rabbits (Leung et al., 1987), rats (Baumbach et al., 1989; Mathews et al., 1989), mice (W. C. Smith et al., 1989), cattle (Hauser et al., 1990), sheep (Adams et al., 1990), and pigs (Cioffi et al., 1990). Based on these studies, the transmembrane ST receptor is a protein of 634 to 638 amino acids with an estimated molecular weight of approximately 70 kDa. Because of similarities in amino acid sequence, the ST receptor is a member of an expanding superfamily of receptor molecules called the cytokine, hematopoietin, or growth hormone/prolactin receptor superfamily (De Meyts, 1992). The extracellular domain consists of about 250 amino acids, the transmembrane domain is comprised of about 25 amino acids, and the intracellular domain has approximately 350 amino acids. A major advance in our understanding of ST

TABLE 2-4 Effects of Somatotropin on Animal Tissue and Systems during Growth or Lactation

Tissue/System	Physiological Effect
Skeletal muscle (growth)	Increased protein accretion; Increased protein synthesis
Mammary tissue (lactation)	Increased synthesis of milk with normal composition; Increased uptake of nutrients used for milk synthesis; Increased activity per secretory cell; Increased maintenance of secretory cells; Increased blood flow consistent with change in milk synthesis
Adipose tissue	Decreased glucose uptake and glucose oxidation; Decreased lipid synthesis, if in positive energy balance; Increased basal lipolysis, if in negative energy balance; Decreased insulin stimulation of glucose metabolism and lipid synthesis; Increased catecholamine stimulated lipolysis; Increased ability of insulin to inhibit lipolysis
Liver	Increased glucose output; Decreased ability of insulin to inhibit gluconeogenesis
Intestine	Increased absorption of calcium and phosphorus required for milk (lactation) or bone (growth); Increased ability of vitamin D (1,25-dihydroxycholecalciferol) to stimulate calcium binding protein; Increased calcium binding protein
Various systems	Increased insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3; Decreased IGFBP-2; Decreased amino acid oxidation and blood urea nitrogen; Decreased glucose clearance; Decreased glucose oxidation; Decreased response to insulin tolerance test; Increased free fatty acid oxidation, if in negative energy balance; Increased cardiac output consistent with increases in milk output (lactation)

NOTE: References are presented in reviews by Peel and Bauman (1987), Etherton (1989a, b), and Bauman et al. (1989b).

action was made when it was discovered that hST binds to two ST receptor extracellular domains (Ultsch et al., 1991; De Vos et al., 1992). The fact that hST mutants that cannot induce dimerization of ST receptors are biologically inactive (De Vos et al., 1992) suggests that this is an important step in initiating the ST signal transduction pathway.

The remainder of this section discusses the mechanisms by which ST exerts its biological effects. The objective here is to provide an overview of the mechanisms; more specific aspects of ST action in domestic animals are discussed in greater detail in numerous reviews (Etherton and Walton, 1986; Peel and Bauman, 1987; Bauman et al., 1989b; Boyd and Bauman, 1989; Etherton 1989a, b; Vernon and Flint, 1989; Bauman and Vernon, 1993).

Lipid Metabolism

Changes in lipid metabolism play an integral role in the responses observed in ST-treated animals. The precipitous decrease in the rate of lipid accretion of meat animals is the most graphic illustration of the profound changes that occur in adipocyte metabolism (Figure 2-2). These metabolic changes are important because they (1) establish the rate of lipid accretion and, therefore, the extent to which ST affects carcass composition in a growing animal; (2) play a key role in redirecting nutrients (e.g., glucose) normally destined to be deposited as lipid to other tissues, thereby supporting the nutrient needs for the increased lean tissue accretion during growth or milk synthesis during lactation; and (3) result in improvements in productive efficiency because of the reduction in the proportion of nutrients used for synthesis of body fat.

Accretion of lipid in adipose tissue is a function of the relative rates of lipid synthesis (lipogenesis) and lipid mobilization. Biological effects of ST on lipid metabolism are not acute (as was previously thought) but rather are chronic, and the extent to which they involve lipogenesis versus lipolysis is a function of energy balance. When animals are in positive energy balance ST causes a reduction in rates of lipid synthesis, whereas effects on rates of lipolysis are minimal (Etherton and Walton, 1986; Walton and Etherton, 1986; Sechen et al., 1989a; Dunshea et al., 1992b). This represents the typical situation for growing animals treated with ST but is also observed for bST treatment of lactating cows that are in substantial positive energy balance. In contrast, when animals are in negative energy balance, rates of lipogenesis are already low and ST treatment affects adipose tissue by increasing rates of lipid mobilization (Machlin, 1972; Eisemann et al., 1986a; Bauman et al., 1988). This situation typically occurs in early lactation in dairy cows during the first weeks of treatment (prior to the increase in voluntary intake), but it can also be observed in growing animals when caloric intake is restricted.

In growing pigs, ST affects lipid synthesis in two ways: (1) there is a striking decrease in both glucose uptake and use of glucose for lipid synthesis by adipocytes; (2) the stimulatory effects of insulin on glucose uptake and metabolism are attenuated (Etherton and Smith, 1991; Etherton and Louveau, 1992). Studies conducted with pig adipose tissue cultured in the presence of pST (Walton et al., 1986) or obtained from pST-treated pigs (Walton and Etherton, 1987; Walton et al., 1987; Magri et al., 1990) and in vivo kinetic studies (Dunshea et al., 1992c) have shown that pST markedly decreases glucose uptake, lipogenic enzyme activities, and lipogenic rate. Studies with ovine and bovine adipose tissue cultured with bST (in which acetate incorporation has been studied) have also shown that bST decreases lipogenesis (Vernon, 1982; Etherton et al., 1987a). Thus, the decrease in nutrient utilization for lipid synthesis in adipose tissue enables nutrients to be redirected to other tissues to support the increases in lean tissue growth or milk synthesis.

One of the important regulatory effects of ST is to alter the response of adipose tissue to homeostatic signals. In growing pigs, pST decreases the stimulatory effects of insulin on glucose uptake and utilization by adipose tissue (Walton et al., 1987; Magri et al., 1990) and decreases whole-body response when insulin tolerance tests are conducted (Gopinath and Etherton, 1989b; Wray-Cahen et al., 1990, 1991). This decrease in insulin sensitivity is not associated with any change in insulin binding or insulin receptor tyrosine kinase activity in pig adipocytes (Magri et al., 1990). ST treatment also causes increased lipolytic responses to epinephrine in growing pigs (Wray-Cahen et al., 1991; Novakofski et al., 1988), steers (Peters, 1986; Boisclair et al., 1989b), and lactating cows (McCutcheon and Bauman, 1986; Sechen et al., 1989b, 1990). Other studies have shown that the antilipolytic effects of insulin are increased by bST and that glucose uptake response to insulin in lactating dairy cows is decreased (Sechen et al., 1989b, 1990).

As previously mentioned, changes in lipid metabolism of the bST-treated cow differ somewhat from changes observed for ST treatment of growing animals, and the differences are a function of energy balance. When bST treatment causes cows to be in negative energy balance, lipid mobilization is increased as illustrated by decreases in body fat, chronic elevations of nonesterified fatty acids (NEFA), and increases in milk fat percent and the proportion of long-chain fatty acids found in milk (Bitman et al., 1984; Eppard et al., 1985; Brown et al., 1989). In this situation, the irreversible loss rate (ILR) of NEFA is increased in a manner that is proportional to the extent the cow is in negative energy balance (Bauman et al., 1988). The increase in ILR of NEFA facilitates the decrease in glucose oxidation observed in dairy cows as will be discussed later.

When bST-treated cows are in positive energy balance, adipose tissue lipogenesis is decreased; however, there is no change in NEFA ILR, milk fat percent, or milk fatty acid composition (Eppard et al., 1985; Sechen et al., 1989a). During

chronic bST treatment, feed intake increases; this is associated with a gradual adjustment in lipogenesis that enables the cow to replenish body reserves over the lactation cycle.

It is important to understand that the biological effects of ST are chronic rather than acute. The effects of ST are not observed in short-term (2 hour) incubations with adipose tissue but only become apparent after 24 hours (Walton and Etherton, 1986, 1987; Walton et al., 1986). This suggests that ST acts to inhibit nutrient utilization in adipose tissue by changing the mass of glucose transporter proteins and/or key lipogenic enzymes either by transcriptional or post-transcriptional regulation. Recent evidence provides support for this hypothesis. Mildner and Clarke (1991) have shown that pST decreases fatty acid synthase mRNA levels by 75 percent in pig adipose tissue. Furthermore, when pigs are treated with pST for 7 days, there is a 20 to 40 percent decrease in glucose transporter (GLUT4) mRNA levels in adipose tissue and an associated 40 percent decrease in GLUT4 protein (Etherton and Louveau, 1992). Other studies also have shown that ST decreases acetyl CoA carboxylase activity in cultured sheep adipose tissue (Vernon et al., 1991) and that in vivo ST treatment of lactating cows (Lanna et al., 1992) and pigs (Harris et al., 1990; Liu et al., 1991) reduces enzyme activity. The fact that ST reduces acetyl CoA carboxylase, fatty acid synthase, and GLUT4 mRNA abundance in adipose suggests that ST affects lipid metabolism by altering transcription of these key metabolic genes. Because insulin sensitivity of adipose tissue is reduced and these genes are insulin regulated, it appears that ST acts, in part, by impeding the insulin signal pathway(s), which results in a diminution in transcription of insulin-regulated genes. This insulin antagonistic effect of ST, however, does not appear to universally affect all insulin-regulated genes, since some of the effects (i.e., antilipolytic) of insulin are not reduced by ST (Sechen et al., 1989a, 1990).

During the past 10 years there has been a remarkable increase in our understanding of the physiological effects that ST exerts on adipose tissue of domestic animals. Despite this, little is known about the ST intracellular signal pathway(s) that cause these alterations in lipid metabolism. Furthermore, it remains unclear how the metabolic changes that occur in adipose tissue in response to ST are coordinated with those that take place in the liver, muscle, mammary tissue, and other tissues to effect the remarkable increases in production observed.

Carbohydrate Metabolism

ST has numerous effects on carbohydrate metabolism (see Table 2-4). This is of particular importance in the dairy cow, in which glucose originates from gluconeogenesis and typically 60 to 85 percent of the glucose turnover is used for milk synthesis. Treatment of cows with bST increases glucose ILR and reduces whole-body glucose oxidation (Bauman et al., 1988). The increase in glucose ILR is the result of an increase in hepatic gluconeogenesis (Pocius and Herbein, 1986; Cohick et al., 1989; Knapp et al., 1992) and one of the tissues that reduces its use of glucose is the hind limb muscle (McDowell et al., 1987). Adaptations in glucose production and oxidation in bST-treated cows are quantitatively equal to the extra glucose required for the increased milk synthesis (Bauman et al., 1988). In pigs (in the postabsorptive state) treated with pST, there is also an increase in hepatic output of glucose (Gopinath and Etherton, 1989b). In both cattle and pigs, liver responses to insulin are decreased (Boisclair et al., 1989a; Gopinath and Etherton, 1989b). In bST-treated lactating cows this is particularly important because the liver is the predominant source of glucose for milk synthesis, and insulin acts to inhibit hepatic production of glucose. Thus, the reduction in hepatic response to insulin allows the liver to sustain the increased rate of gluconeogenesis that is critical to support the increase in milk synthesis.

When pigs are treated chronically with pST, plasma glucose and insulin concentrations are elevated (Gopinath and Etherton, 1989a; Dunshea et al., 1992a). The increase in plasma glucose is most likely related to a reduction in glucose uptake, particularly by adipose tissue. Because a significant quantity of glucose is metabolized in adipose tissue of pigs, a decrease in glucose utilization by adipose tissue redirects a considerable quantity of glucose to other tissues. For example, it has been shown that approximately 40 percent of whole-body glucose uptake measured in the basal state and 25 to 30 percent measured in the insulin-stimulated state are used by adipose tissue of barrows (Dunshea et al., 1992c). In contrast, glucose utilization by adipose tissue of pST-treated pigs amounts to only about 7 percent of whole-body glucose turnover (Dunshea et al., 1992c).

Protein Metabolism

Less is known about the effects of ST on protein metabolism than about either lipid or carbohydrate metabolism. It is clear the ST treatment increases muscle protein deposition in growing animals and milk protein secretion in lactating cows. No studies have examined the effects of ST on the kinetics of protein metabolism during ST treatment in dairy cows. In growing pigs and cattle, one of the most characteristic responses to ST treatment is a dose-dependent decrease in blood urea nitrogen concentration. This suggests that whole-body oxidation of amino acids and the concomitant hepatic conversion of ammonia to urea are reduced. These adaptations in amino acid metabolism are consistent with an increased use of amino acids for protein accretion.

The kinetics of amino acid metabolism have been examined in growing cattle treated with bST. Eisemann et al. (1986a,b) have reported that ST treatment of beef heifers fed slightly more than maintenance amount increased nitrogen

retention and whole-body protein synthesis without affecting protein degradation. Subsequently, Eisemann et al. (1989b) reexamined this in rapidly growing steers and found that bST treatment increased L-[^{14}C]-leucine use for protein synthesis and that whole-body rates of leucine oxidation decreased. Furthermore, they noted that the additional nitrogen retained was deposited with an incremental efficiency of approximately 50 percent. Other studies with growing lambs and cattle have demonstrated that the fractional rate of protein synthesis is increased in skeletal muscle with bST treatment (Pell and Bates, 1987; Eisemann et al., 1989a). A recent study with growing pigs indicates that pST treatment increased rates of whole-body protein turnover; however, the absolute increment in protein synthesis rate was greater than that for breakdown, leading to the increased net nitrogen retention (Tomas et al., 1992).

One of the critical events that occurs during postnatal muscle growth is an increase in muscle DNA content. This event is important because postnatal accretion of DNA is a key factor in regulating muscle growth (Allen, 1988). This increase is caused by proliferation of satellite cells that reside between the sarcolemma and basement membrane of myofibers. These cells have the ability to fuse with the myofiber and thereby contribute their nucleus to the cell. Thus, during postnatal muscle growth the increase in muscle DNA is coordinated with the increase in muscle protein. As discussed above, ST increases the rate of protein accretion markedly. The effects of ST appear to be not only caused by changes in protein metabolism but also by changes in the rate of satellite cell proliferation. One of the growth factors that has been shown to stimulate proliferation of satellite cells is IGF-I (Allen, 1988). This observation is significant because the mitogenic effects of ST are mediated indirectly by IGF-I (Florini, 1987).

Mammary Gland Metabolism

Administration of bST to lactating dairy cows results in major adaptations in mammary tissue metabolism. The change that occurs in the shape of the lactation curve with long-term bST administration indicates that the number of secretory cells in the glands and/or the synthetic capacity of each mammary epithelial cell must increase (Bauman et al., 1985). Recent studies with lactating goats have demonstrated that bST treatment prevented the normal decline in mammary cell number and increased the activity of key enzymes involved in milk synthesis (22 weeks; 27 percent increase in milk yield) (Knight et al., 1990). Baldwin (1990) demonstrated that bST-treated cows had increased RNA per mammary gland, indicating an increase in protein synthetic capacity. In addition, scientists have reported significant increases or trends for increases in activities of several enzymes from bST-treated cows and goats (Baldwin, 1990; Knight et al., 1990, 1992).

A major paradox is that bST does not appear to directly mediate its effects on the mammary gland. bST does not have any direct effect on milk synthesis in bovine mammary tissue in vitro (Gertler et al., 1983) and bovine mammary cells appear to lack bST receptors (Akers, 1985; Collier et al., 1989). However, this is not completely resolved; some recent studies have reported mRNA for somatotropin receptors in mammary tissue from several species including cows (Glimm et al., 1990; Jammes et al., 1991). There has been some suggestion that IGF-I may mediate the galactopoietic effects of bST because bovine mammary epithelial cells do have receptors for IGF-I (Collier et al., 1989). Prosser et al. (1989) reported that infusion of IGF-I (1.1 nMol/min) for 6 hours into the pudic artery of lactating goats increased milk secretion by 30 percent. Recently, Davis et al. (1989) conducted a study in which IGF-I was infused (43 nMol/hour via jugular catheter) into lactating goats on days 4 to 6 of a 10-day experimental period. Although bST administration increased milk production, there was no increase in milk yield of the group infused with IGF-I, even though blood concentrations of IGF-I were comparable between the two groups. An additional complication is that IGFs in physiological fluids are bound to soluble, high-affinity IGF-binding proteins (IGFBP). Although we do not have a clear understanding of how the IGF complex is able to mediate mammary function, it is apparent that changes in circulating concentrations of IGF-I and some of the IGFBP are closely tracking the biological events and magnitude of milk responses that occur with bST treatment (see review by Bauman and Vernon, 1993).

Consistent with the increases in milk yield, bST treatment has been shown to increase cardiac output and mammary blood flow (Mepham et al., 1984; Davis et al., 1988; Fullerton et al., 1989). Based on current concepts of mammary biology, it is probable that the alteration in blood flow is a consequence of changes in mammary tissue metabolism rather than the cause of these changes.

Summary of Effects of Somatotropins

Somatotropins alter an array of physiological processes in domestic animals treated chronically with the hormone. These effects are precisely coordinated to alter the flow of nutrients among the tissues of the body. ST alters many metabolic pathways in numerous tissues and changes tissue responses to other endocrine signals. Overall, these alterations in metabolism and cell proliferation lead to the production responses observed in meat and dairy animals. It is likely that as we increase our understanding of how ST functions, we will be able to develop ways to further potentiate the stimulatory effects of ST or identify alternative strategies that increase not only growth performance and milk yield but, more important, the efficiency of production.

β-ADRENERGIC AGONISTS

Synthetic compounds called *β*-adrenergic agonists exhibit profound effects on growth and metabolism of skeletal muscle and adipose tissue. They share some similarity in structure and function with the naturally occurring catecholamines. Three major catecholamines (dopamine, norepinephrine, and epinephrine) are found in mammals. They circulate in the blood plasma, can act at sites removed from their origin (a relationship that is used to define a hormone), and regulate a wide range of physiological responses in many tissues. Epinephrine in particular, but also norepinephrine, are major regulators of metabolism. Examples of the various physiological actions of catecholamines include the following: regulation of the speed and force of heart contractility, motility and secretory responses of various portions of the gastrointestinal tract, bronchodilation, salivary gland and pancreatic insulin secretion, blood vessel constriction and dilation, uterine contraction, and spleen capsule contraction.

The three endogenous catecholamines are related in structure, biosynthetic sequence, and function. General information regarding catecholamine structure, biosynthesis, metabolism, and adrenergic control of physiological and metabolic function has been reviewed (Martin, 1985; Norman and Litwack, 1987; Timmerman, 1987; Mersmann, 1989b; Weiner and Molinoff, 1989; Hoffman and Lefkowitz, 1990). The chemical structures of dopamine, norepinephrine, and epinephrine are presented in Figure 2-3. Epinephrine is the primary hormone secreted by the adrenal medulla.

External stimuli cause the adrenal medulla to release epinephrine and rapidly elevate the peripheral concentration. Stimulation can cause the release of some norepinephrine from the adrenal medulla as well. The relative plasma concentration of these two naturally occurring catecholamines varies among different species. Norepinephrine is usually present at two-to-five times the concentration of epinephrine under resting conditions, whereas dopamine is present at similar or lower concentrations than epinephrine in most mammalian species (Buhler et al., 1978).

All three catecholamines, but particularly norepinephrine and epinephrine, precipitate an extremely large spectrum of physiological functions either by stimulating central nervous system synaptic activity or direct innervation of an organ by the sympathetic nervous system or by acting as plasma hormones. Response to catecholamines requires the presence of a receptor that will bind the particular neurotransmitter or hormone whose concentration has been increased and then couple the receptor binding to an effective intracellular response system. Because most organs of the mammalian body possess receptors for catecholamines, these substances have a major role in regulating many metabolic processes. For example, catecholamines are instrumental in stimulation of glycogen phosphorylase and inhibition of glycogen synthase to stimulate the production of glucose from glycogen stores. Catecholamines also stimulate lipolysis to cause the release of free fatty acids from adipose tissue triacylglycerol stores. Thus, catecholamines have a role in control of plasma concentrations of two primary oxidative substrates—glucose and free fatty acids.

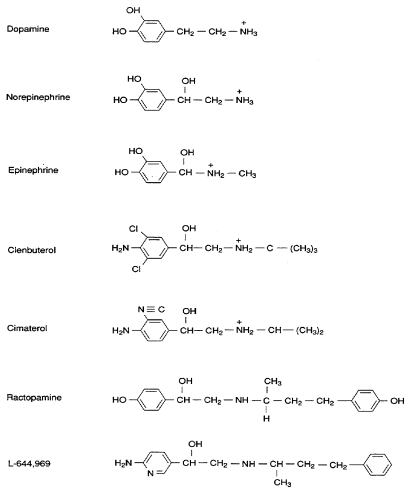

FIGURE 2-3
Chemical structures of the endogenous catecholamines dopamine, norepinephrine, and epinephrine and of select synthetic *β*-adrenergic agonists.

Adrenergic Receptors

The many and sometimes antipodal functions regulated by the naturally occurring catecholamines lead to the concept that different receptors must exist in different organs. For example, norepinephrine stimulates mammalian heart contractility at a lower concentration than epinephrine, whereas epinephrine is more potent for stimulation of spleen capsule contraction. Observations such as this led to the concept of distinct α- and α-adrenergic receptors that control various physiological and metabolic functions. This type

of classification was aided by the synthesis of a large number of analogs of norepinephrine. As the number of analogs increased, compounds became available that would preferentially stimulate (or inhibit) a particular function. With an increased spectrum of norepinephrine analogs and continued investigation of the adrenergic control of additional biological functions, it became appropriate to divide the *β*-adrenergic receptor class into *β*-1 and *β*-2 subclasses. Eventually, the *β*-adrenergic receptor class was divided into *β*-1 and *β*-2 subclasses. These classification schemes for adrenergic receptors are attempts to codify biological responses so that the complex functions and plethora of chemical structures can be integrated into a rational pattern.

There have been attempts to establish additional subclasses of receptors based on pharmacological properties and distribution of both α- and α-receptors (Martin, 1985; Norman and Litwack, 1987; Timmerman, 1987; Mersmann, 1989a; Weiner and Molinoff, 1989; Hoffman and Lefkowitz, 1990). Protein purification techniques (Lefkowitz and Caron, 1988) and molecular biology techniques using nucleotide sequences of cDNAs have definitively established the existence of distinct α-1- (Cotecchia et al., 1988), α-2-(Kobilka et al., 1987b), α-1- (Machida et al., 1990), and α-2-(Kobilka et al., 1987a) adrenergic receptors. Molecular characterization of the human α-3-receptor has also been reported (Emorine et al., 1989). It is too early to know the extent of homology between receptor types purported to be α-1- (or α-2- and α-3-) adrenergic receptors when examined in the same tissue in a number of species or in a variety of tissues within a single species.

It is important to note that earlier attempts to classify adrenergic receptors, agonists, and antagonists was confounded by arbitrary selection of ligands, choice of variable biochemical or physiological events, and use of discrete "all-or-none" response criteria. These physiological data are complemented by ligand binding studies in some but not all cases. In addition, ligand binding can be affected by subtle differences among the same cell type across species or in different cell types within a given species. Receptor classification becomes extremely confounded by use of a variety of species, a multiplicity of analogs, several diverse cell types, and numerous experimental approaches (McGonigle et al., 1986; Neve et al., 1986; Timmerman, 1987; Mersmann, 1989b; Lafontan et al., 1990). Although most of the synthetic adrenergic agonists found to exhibit repartitioning effects on growth of mammalian species have been characterized as *β*-agonists; whether their effects are directly mediated through the *β*-receptors is equivocal.

Distribution of adrenergic receptor types is of equal importance in determining the nature or magnitude of a response. It has become apparent that many or even most mammalian organs, tissues, or cell types do not have a pure population of α- or α-adrenergic receptors; rather a mixture of subtypes of these receptors is usually present, albeit at different levels (Minneman et al., 1979). For example, heart contractility usually is considered to be stimulated by α-1-adrenergic receptors, although mammalian heart muscle appears to have both α-1-and α-2-adrenergic receptors. The proportion may vary from essentially 100 percent α-1-adrenergic receptors in the guinea pig ventricle (Hedberg et al., 1980) to 35 percent α-2-adrenergic receptors in the human ventricle (Heitz et al., 1983).

Skeletal muscle has *β*-adrenergic receptors as evidenced by the stimulation of glycogenolysis and the production of lactate by epinephrine, norepinephrine, and the analog isoproterenol both in vitro and in vivo. The antagonist propranolol inhibits this response. More direct measurement of *β*-adrenergic receptors by ligand binding techniques also indicates the presence of *β*-receptors, with the *β*-2 subtype predominating over the *β*-1 subtype (Liggett et al., 1988). Expression of *β*-3-receptor mRNA has been demonstrated in rat skeletal muscle (soleus), as well as adipose, liver, and ileum, but was not observed in brain, skin, heart, and lung (Emorine et al., 1989). Two *β*-adrenergic agonists that dramatically enhance skeletal muscle deposition, clenbuterol and cimaterol, are purportedly specific for the *β*-2-receptor subtype (O'Donnell, 1976; Kim and Sainz, 1990), whereas ractopamine is primarily a *β*-1-agonist (Anderson et al., 1991).

Mammalian adipose tissue cells contain *β*-adrenergic receptors as indicated by stimulation of lipid breakdown (lipolysis) by epinephrine, norepinephrine, and isoproterenol as well as a number of other norepinephrine analogs both in vitro and in vivo. These effects can be antagonized by propranolol or other β-adrenergic antagonists. Lipogenesis, both fatty acid and triacylglycerol biosynthesis in the adipocyte, is inhibited by *β*-adrenergic agonists and such effects can be antagonized by *β*-adrenergic antagonists (Fain and Garcia-Sainz, 1983; Buttery and Dawson, 1987; Timmerman, 1987; Mersmann, 1989a; Yang and McElligott, 1989). Establishment of the *β*-adrenergic receptor subtypes on the mammalian adipocyte has not been particularly successful. Some studies have indicated the receptor is of the *β*-1-adrenergic subtype, others indicate a mixture of *β*-1- and *β*-2-adrenergic receptors, and yet others indicate that a totally different receptor, the *β*-3-adrenergic receptor, is also present (Emorine et al., 1989; Lafontan et al., 1990). How much of the diversity in description of the adipose tissue adrenergic receptor subtypes is the result of studies in different species, use of different agonists and antagonists, or use of different methodologies, including ligand binding compared to measurement of cellular function, is not yet understood.

Effects of β-Adrenergic Agonists on Growth and Carcass Composition

Since the early 1980s, several synthetic analogs of epinephrine and norepinephrine have been investigated for their

ability to promote skeletal muscle growth and reduce the fat content of animal carcasses. These orally active materials are usually referred to as β-agonists. Structures of some of the compounds that have been studied and for which effects have been reported in the literature are shown in Figure 2-3. These substances bind predominantly to β-receptors found in the membranes of cells. There are relatively few substances that bind almost exclusively to one type of receptor. Several of the agonists currently being evaluated for use as metabolic modifiers in the livestock industry show a marked specificity toward the β-2-receptor; stimulation of the β-1-receptor results in tachycardia. Transient increases in heart rate and systemic blood flow are observed with dietary administration of cimaterol in lambs (Beermann, 1987) and clenbuterol in cattle (Eisemann et al., 1988).

The β-adrenergic agonists reported in the literature as potential metabolic modifiers are all orally active, unlike ST and most of the anabolic steroids. Their main effects on the carcass are to increase skeletal muscle and reduce adipose tissue mass, with little or no effect on bone. This is sometimes accompanied by an increase in growth rate or feed efficiency. It is not surprising, then, that responses in live-weight gain and feed efficiency are related to the dose rate, with indications that efficacy is reduced at extremely high doses (Ricks et al., 1984; Hanrahan et al., 1986; Reeds et al., 1986). Effects on the overall body weight are of course markedly influenced by the relative changes in fat and muscle, which are in turn influenced by the dose. Mass of visceral tissues and most organs is not increased; in some cases liver mass is decreased. Therefore, percent of live weight present in the carcass is usually increased. All farm animal species tested (including poultry, ruminants, and pigs) show similar but variable effects (see Table 2-5).

In mammals the magnitude of the response generally appears to be greater in ruminants than in single-stomached animals, although a functioning rumen does not appear to be required in calves (Williams et al., 1987) or lambs (Williams et al., 1989). The 20 to 40 percent increases in skeletal muscle mass commonly observed in growing lambs and cattle are rarely observed in swine (see reviews by Hanrahan et al., 1987; Beermann, 1989, 1993; Anderson et al., 1991; Moloney et al., 1990). Likewise, the 20 to 40 percent reductions in adipose tissue mass observed in lambs and cattle are approximately half as large in pigs.

The magnitude of the influence of these compounds on the adipose tissue content of the carcass appears to be related to the tendency of the control animals to lay down fat (i.e., the magnitude of carcass or empty-body lipid accretion rate). Responses are less significant in preweaning and young rapidly growing animals, in which lipid accretion rates are low. Likewise, the enhancement of skeletal muscle growth is also less in these younger animals. Jones et al. (1985) and Moser et al. (1986) studied the impact of cimaterol dose on pigs treated from approximately 60 to 105

TABLE 2-5 Representative Responses in Farm Animal Species to Dietary Administration of β-Adrenergic Agonists

	Response, percent		
Variable	Poultry	Ruminants	Swine
Growth rate	4	0-20	0-10
Feed conversion	5	0-20	0-15
Carcass protein	6	5-25	4-15
Carcass lipid	-4 to -8	-15 to -40	-5 to -25

NOTE: Magnitudes of response are summarized from the following publications and reviews: Hanrahan et al. (1987), Williams (1987), Beermann (1989, 1993), Moloney et al. (1990), and Anderson et al. (1991).

kg BW. Effects on average daily gain and feed efficiency were small, but dressing percentage was increased and carcasses contained up to 10 percent less fat and 10 percent more skeletal muscle in proportion to cimaterol dose. More recent studies with another compound, ractopamine, have demonstrated 5 to 20 percent improvements in growth performance and dose-dependent improvements in carcass composition, including 8 to 20 percent more muscle mass (Adeola et al., 1990; Watkins et al., 1990; Bark et al., 1992) and 4 to 37 percent less adipose tissue (Watkins et al., 1990; Bark et al., 1992). Although cimaterol was effective in finishing pigs, it had no effect on growth performance or carcass composition in younger pigs fed similar doses from 10 to 60 kg BW (Mersmann et al., 1987); nor were there any effects on the several indices of lipid metabolism studied. Similar differential responses between young and older animals have been observed in ruminants. The dose-response effects of cimaterol (Quirke et al., 1988) and L-644,969 (Moloney et al., 1990) on growth performance and carcass composition in finishing cattle exceed the magnitude of response seen in veal calves (Williams et al., 1987). Effects on skeletal muscle growth of 10-day-old lambs (15 kg BW) fed milk replacer and cimaterol for 21 days (Williams et al., 1989) was minimal (10 to 15 percent), approximately half the reduction in lipid accretion rate as that observed with similar treatment in older ruminating lambs from the same genetic pool (O'Connor et al., 1991).

The lack of response in very young ruminants and nonruminants may be related to fewer receptors, lower binding affinity, or more rapid development of refractoriness to these compounds. Kim and Sainz (1990) have shown that the number of β-receptors in rat plantaris muscles decreased 28 to 42 percent after 3 days of dietary cimaterol administration, which preceded the attenuation of the muscle hypertrophy response over a 14-day treatment period.

There have been relatively few specific breed or genotype comparison studies reported for effects of β-agonists in farm livestock. Either little evidence of important genotype-by-treatment interactions or none at all has been reported

for lambs (Hanrahan et al., 1987) and pigs (Yen et al., 1990a,b; 1991). However, significant differences in responses among genotypes were observed in some comparisons (Warris et al., 1990; Gu et al., 1991a,b; Bark et al., 1992). Cimaterol and ractopamine increased skeletal muscle growth in both obese and lean genotypes of swine (Yen et al., 1990a,b; 1991), but anabolic responses to ractopamine were greater in genotypes that exhibited superior growth performance and carcass muscle and protein accretion rates than the inferior genotype to which they were compared (Bark et al., 1992; Gu et al., 1991b). Ractopamine-treated pigs of the inferior genotype still exhibited 12 kg less skeletal muscle mass than control pigs from the superior genotype when comparisons were made at similar body weights (Bark et al., 1992), which indicates that genotypic differences are not eliminated by *β*-agonist administration.

Responses to *β*-agonists in poultry tend to be, on a percentage basis, less significant than those seen in the mammals (see Table 2-5). This difference is probably caused by fundamental differences between adipose tissue metabolism and the type of *β*-receptor found in the muscle. There is, however, some evidence for the response in chickens to be related to the sex of the animal. Treatment of Hubbard × Hubbard broilers with cimaterol reduced carcass fat on the order of 10 percent in the female birds but only approximately 5 percent in the males (Dalrymple and Ingle, 1987). This sexual dimorphic effect may be caused by the tendency of female broilers to deposit more fat than their male counterparts. Cimaterol fed at 1 mg/kg to broiler chickens increased leg muscle weight more than breast muscle weight, and effects were greater after 56 days of treatment than after 38 days (Morgan et al., 1989). Cimaterol has also been shown to improve growth performance and body composition of ducks in a dose-dependent manner (W. F. Dean, Duck Research Laboratory, Eastport, Long Island, N.Y., personal communication, 1987). Ractopamine causes a dose-dependent improvement in growth performance, dressing percentage, and muscle content of turkeys when administered at the end of the feeding period (12 to 20 weeks) (Wellenreiter and Tonkinson, 1990a,b).

Mechanisms of β-Agonist Action

Although it is convenient to discuss en masse the *β*-agonists that seem to induce enhancement of skeletal muscle deposition and reduce carcass fat content, it should be remembered that marked differences are present in their structures, pharmacokinetics, and metabolism. Therefore, some differences in their mode of action and efficacy are to be expected.

The pharmacokinetic properties of *β*-adrenergic agonists will influence rates of absorption into the circulation, magnitude and temporal pattern of elevated concentrations in blood or plasma, and even selectivity for specific *β*-receptors (Timmerman, 1987). Variation among the compounds in how they are metabolized and eliminated from the circulation gives rise to estimated biological half-lives in rats ranging from 2 hours for fenoterol (Rominger and Pollmann, 1972) to 24 hours for clenbuterol (Kopitar and Zimmer, 1976). Species and mode of administration also contribute to variation among half-life estimates of the *β*-agonists. Published estimates of half-lives of *β*-agonists in farm animals are scarce. Affinity chromatography and high-performance liquid chromatography were used to describe the biphasic decline of plasma cimaterol concentration following a bolus intravenous injection in steers and yielded half-life estimates of 2.5 minutes for the distribution phase and 54 minutes for the elimination phase (Byrem et al., 1993). Biphasic elimination of clenbuterol in urine was demonstrated in veal calves fed 5 µg/kg BW twice daily for 3 weeks (Meyer and Rinke, 1991). Estimated half-life was 10 hours for the rapid phase and 2.5 days for the second phase. Half-life of clenbuterol in plasma could only be calculated for the fast phase and was estimated to be 18 hours. These estimates as well as those for other synthetic *β*-agonists developed for therapeutic use are much larger than for epinephrine and indicate that transfer to the peripheral compartment is very rapid. They also provide evidence that direct metabolic effects of cimaterol on specific tissues may be studied by close arterial infusion of cimaterol into specific vascular beds.

No formal proof exists for a common or shared set of specific actions of these compounds on skeletal muscle growth or lipid metabolism among all species in which they have been evaluated. The similar changes observed in protein and lipid deposition in growing animals suggest involvement of common effects. However, differences exist among the results of studies on mode of action. Review of the literature indicates that both quantitative and qualitative differences exist in the lipid metabolism response of different species to the same compound and of the same species to different compounds (Mersmann, 1989b). Similarly, attempts to block responses in muscle and adipose with receptor-specific compounds have given mixed results (Reeds et al., 1988; Choo et al., 1989). Therefore, caution must be exercised when drawing generalizations about mode of action of these compounds.

Mode of Action in Skeletal Muscle

Treatment with *β*-agonists causes muscle hypertrophy rather than hyperplasia (Maltin et al., 1986; Beermann et al., 1987; Kim et al., 1987), but the response is not equal or not seen in all muscles (Beermann et al., 1986a; Bohorov et al., 1987; Dawson et al., 1988; Morgan et al., 1989). Responses in muscles containing a predominance of one fiber type (e.g., rat soleus) have been both greater than (Maltin et al., 1986) and equal to (Reeds et al., 1986; Thiel et al., 1987) responses

observed in mixed-fiber type muscles. It is apparent that type-II fibers (i.e., fast-contracting, mixed glycolytic-oxidative) account for the greater portion of hypertrophy when compared with the type-I fibers (slow contracting oxidative) (reviewed by Yang and McElligott, 1989). There is evidence that long-term treatment can cause an increase in the proportions of type-II fibers (Beermann et al., 1987; Zeman et al., 1988), although this has not always been observed (Kim et al., 1987).

Increases in muscle protein deposition (growth) can either be a result of changes in the rate of protein synthesis or in the rate of degradation or both. Several studies suggest that *β*-agonists reduce the rate of muscle protein degradation in sheep (Bohorov et al., 1987), rats (Reeds et al., 1986), cattle (Dawson et al., 1988), and broilers (Morgan et al., 1989). There are also data which suggest that muscle protein synthesis may be enhanced in rats (Emery et al., 1984), lambs (Claeys et al., 1989), cattle (S. B. Smith et al., 1989), and swine (Bergen et al., 1989; Helferich et al., 1990). Chronic feeding of clenbuterol increased the rate of *β*-amino nitrogen uptake by 44 percent in the hindquarters of steers (Eisemann et al., 1988). This was caused by chronic elevation of blood flow with no difference in arterio-venous concentration. Plasma urea nitrogen concentrations were reduced 20 percent with chronic cimaterol treatment. These data are consistent with an increase in protein synthesis and deposition and reduced amino acid oxidation with chronic administration of clenbuterol. Although oxygen utilization by the hindquarters was also increased, glucose uptake was not, indicating greater reliance on lipid oxidation to support the expected increase in energy required for protein synthesis and deposition.

Attempts to use isolated muscle preparations have also yielded equivocal results. For example, using two muscle cell lines, L6 and G8-1, Harper et al. (1990) obtained an increase in protein synthesis of about 12 percent following treatment with cimaterol, with the half-maximal effect occurring at a concentration consistent with the binding of cimaterol to the *β*-receptor on the cells. The effect was blocked by the antagonist propranolol. As mentioned earlier, Kim and Sainz (1990) demonstrated a temporal reduction of the number of *β*-receptors in rat muscle with cimaterol treatment, which preceded a diminished response in muscle hypertrophy during a 14-day treatment period. These data are taken as indicative of the involvement of the β-receptor. The presence of the *β*-receptor on L6 myoblasts (Pittman and Molinoff, 1983) and in muscle suggests that the agonists do have a direct effect on the muscle, especially in light of the finding that treatment of animals with propranolol (a *β*-antagonist) can block the myogenic action of *β*-agonists (MacLennan and Edwards, 1989).

Young et al. (1990) observed a 25 percent increase in the quantity of myofibrillar protein and a 30 percent increase in the quantity of myosin heavy chain in primary muscle cell cultures of broiler chicks with 10^{-7} M cimaterol. At higher levels of cimaterol the myosin heavy chain synthesis rate was increased 10 to 12 percent and protein degradation rate was decreased 10 to 15 percent. Clenbuterol (10^{-7}) increased fusion rate and protein synthesis rate in neonatal rat myoblast cultures but failed to exhibit similar effects in rat satellite cell cultures or cultures of L6 myoblasts and myotubes and had no effect on neonatal fibroblast cultures (McMillan et al., 1992). McElligott et al. (1989) also observed no effect on protein metabolism of L6 cells treated with the agonist zinterol. It appears that origin and/or presence of the full complement of regulatory factor genes (present in animal-derived cells) may be important in responsiveness of myogenic cells to the synthetic *β*-agonists.

Taking an overview of the literature, it would appear that the rate of muscle protein synthesis is increased and the protein degradation rate may be reduced in animals fed these synthetic *β*-agonists. Temporal patterns of change are present that make it difficult to ascertain which might be the major route by which *β*-agonists increase the rate of muscle protein deposition. Measurement of calcium-dependent proteinase, calpastatin, and cathepsin activities in skeletal muscle of *β*-agonist-treated sheep (Higgins et al., 1988; Wang and Beermann, 1988; Beermann et al., 1989; Kretchmar et al., 1990), cattle (Wheeler and Koohmaraie, 1992), rabbits (Forsberg et al., 1989), and broiler chickens (Morgan et al., 1989) indicate that activities of calpastatin are increased and/or the microcalpain protease activity is reduced with cimaterol, L-644,969, and L-665,871 adrenergic agonist administration in vivo. The protein-sparing effects of *β*-agonist administration have been demonstrated in response to restricted energy intake and starvation. Cimaterol converted a daily loss of 2.3 g carcass protein to a daily gain of 4.1 g carcass protein in lambs maintained at zero energy balance (Kim et al., 1989). Starvation-induced skeletal muscle atrophy was significantly reduced when clenbuterol was given to rats (Choo et al., 1990). Indications that clenbuterol-induced reduction in basal nitrogen loss could be achieved in sheep (Hovell et al., 1989) have subsequently been shown in further studies to be transient, and nitrogen loss was equal in control and treated sheep after a 4-day treatment period (Inkster et al., 1989).

Indirect Effects of β-Adrenergic Agonists

Despite evidence for direct, receptor-mediated influences on skeletal muscle, it is possible that some of the changes in muscle protein metabolism in vivo are brought about by an indirect mechanism, that is, as a result of the changes in the circulating concentrations of some endogenous hormones (see review by Buttery and Dawson, 1987). Elevation of insulin concentrations have been observed in sheep (Beermann et al., 1986b; O'Connor et al., 1988) and cattle (M. Vestergaard, National Institute of Animal Science,

Tjele, Denmark, personal communication, 1990) with acute administration of cimaterol, but chronic treatment reduces insulin concentrations 25 to 50 percent (Beermann et al., 1987; O'Connor et al., 1988). Circulating levels of ST are not elevated with acute or chronic exposure of growing lambs to cimaterol (O'Connor et al., 1988), and no difference was observed in plasma concentrations of prolactin, cortisol, or thyroid hormones at 6 or 12 weeks. Similar results have been reported for growing steers fed cimaterol (Chikhou et al., 1991).

Cimaterol evokes similar stimulation of skeletal muscle growth and reduction in lipid accretion in animals surgically manipulated to remove the source of somatotrophic and metabolic hormone secretion. Cimaterol administration causes marked muscle hypertrophy in hypophysectomized rats (Thiel et al., 1987) and thyroidectomized rats (Forsberg and Wehr, 1990), and muscle hypertrophy is stimulated in severely diabetic rats and diabetic rats given a daily fixed dose of insulin (McElligott et al., 1987). These data suggest that ST, the thyroid hormones, and insulin, all important metabolic hormones required for normal muscle growth, are not involved to any great extent in the mediation of β-agonist-induced skeletal muscle hypertrophy. These results and the lack of significant changes in circulating metabolic hormone concentrations in response to β-agonist administration suggest that the β-agonist's mode of action involves direct, receptor-mediated stimulation of skeletal muscle growth.

Mode of Action in Adipose Tissue

It is generally accepted that β-agonists act directly on adipose tissue via the β-receptor to stimulate lipolysis. This is supported by the consistent observation of elevated plasma free fatty acids in treated animals (Beermann et al., 1987; Eisemann et al., 1988). Results from in vitro studies have not yielded such clear-cut results. For example, clenbuterol has been shown to stimulate lipolysis in adipose tissue from rats (Duquette and Muir, 1985) and chickens (Campbell and Scanes, 1985) but not pigs (Rule et al., 1987) or cattle (Miller et al., 1988; Dawson et al., 1989). However, isoproterenol, cimaterol, and ractopamine all stimulate lipolysis in pig adipose tissue in vitro (Liu et al., 1989; Peterla and Scanes, 1990). Several reports have shown that β-agonists can also affect the in vitro rate of lipogenesis (Mersmann, 1989a,b; Mills and Liu, 1990; Peterla and Scanes, 1990). In the absence of any effect on lipolysis, some reports have concluded that the reduction in lipogenesis is a very important component in the mechanism whereby total body fat is reduced (Miller et al., 1988). It is becoming clear that the incubation conditions used for these in vitro incubations is critical (Liu et al., 1989; Mersmann, 1989a,b; Mills and Liu, 1990). Liu and Mills (1990) have subsequently shown that clenbuterol and ractopamine reduce insulin binding to porcine adipocytes presumably through reduced insulin receptor number, thereby antagonizing insulin action on porcine adipocytes.

A major deterrent to conclusively identifying the mode of action is that it is difficult to measure rates of lipogenesis in vivo. It is also very likely that potencies differ among β-agonists, especially in terms of their relative effects on lipolysis and lipogenesis as well as the response between different species.

The ability of many β-agonists to induce a decrease in adipose tissue and at the same time an increase in skeletal muscle is a very useful attribute for animal production. However, there are agonists developed for other purposes that reduce adipose tissue without increasing lean mass, for example BRL 35135 (Arch and Ainsworth, 1983; Arch et al., 1984). It therefore seems that the increase in lean mass seen with many β-2-selective agonists is not simply a consequence of the reduced amount of energy stored in adipose tissue.

Interaction between Treatment and Dietary Intake

There have been relatively few reports in which the interaction between response to β-agonists and dietary protein and/or energy intake was investigated. Dry-matter intake is commonly reduced on initial exposure to the β-agonists but most often returns to normal within a short time and remains unchanged thereafter. The repartitioning effects of β-agonists are reported to occur in both adequate and restricted feeding conditions in lambs (Hovell et al., 1989; Kim et al., 1989) and pigs (Bracher-Jakob and Blum, 1990; Bracher-Jakob et al., 1990; Dunshea et al., 1991). However, significant increases in growth rate tend to occur only in well-fed animals. Even these effects can be lost if the animals become refractory to the compound or if the dose rate is increased (see, e.g., the data assembled by Williams, 1987; Beermann, 1993).

Providing adequate supplies of amino acids and energy is prerequisite to optimizing rate and efficiency of protein use for growth in normal management systems and may be particularly important when protein deposition rates are enhanced by β-agonist administration. Increased skeletal muscle protein deposition will increase the requirement for individual amino acids unless there is an increase in the efficiency with which dietary protein (amino acids) is used for growth. Inadequate protein intake constrains the magnitude of improvement in growth performance, nitrogen balance, or the degree to which protein accretion rate or skeletal muscle growth is enhanced by ractopamine in pigs (Anderson et al., 1987; Adeola et al., 1990; Dunshea et al., 1991; Mitchell et al., 1991). Anderson et al. (1987) observed that nitrogen retention in swine fed ractopamine is enhanced with an 18 percent crude protein diet, but nitrogen retention was reduced with a 12 percent protein diet.

Adeola et al. (1990) observed that ractopamine depressed ADG and gain: feed 9 and 10 percent, respectively, when the diet contained only 13 percent crude protein. However, ractopamine increased ADG and gain: feed 10 to 12 percent and 12 to 25 percent, respectively, when the diet contained 17 percent crude protein. These studies do not resolve the question of whether the efficiency of protein utilization is changed or whether protein requirement is increased.

If protein intake limits the rate of protein accretion, either the amount or the profile of amino acids supplied in the diet may account for the restriction of protein deposition. Therefore, in nonruminants protein intake titration experiments must be conducted using diets in which the amino acid profile is matched to the amino acid profile of deposited protein. These types of data are limited. Dunshea et al. (1991) demonstrated in gilts fed diets ranging from 8.3 to 23 percent crude protein concentration that carcass protein accretion rates were not increased by ractopamine at crude protein concentrations below 14 percent, and that additional crude protein was required (16.8 versus 14 percent) to accommodate the greater protein accretion rates achieved with 20 mg ractopamine/kg diet. No evidence was observed for ractopamine increasing the efficiency of protein use for growth. In ruminants, enhanced availability of amino acids does enhance skeletal muscle growth. Substitution of fishmeal for an equal amount of soy protein enhanced skeletal muscle mass in ram lambs by 15 to 19 percent, and effects were additive with cimaterol (Beermann et al., 1986a). Proximal hind limb muscles in lambs fed fishmeal and cimaterol were 40 to 45 percent larger than those in lambs that received no fishmeal or cimaterol.

An increase in skeletal muscle mass and in the basal metabolic rate of treated animals (see, e.g., MacRae et al., 1988; Kim et al., 1989) may increase the maintenance requirement of animals fed β-agonists. These increases would be offset only minimally by the reduction in fat deposition, but the shift of protein synthesis and accretion away from tissues with higher turnover rates (small intestine and liver) and toward skeletal muscle may help minimize changes in maintenance requirements. Although it is possible to speculate on the magnitude of any changes in nutrient response following treatment with β-agonists, it is doubtful that data are available to do this with any precision. In extrapolating from the data available for ST-treated animals, caution must be exercised because although both ST and β-agonists have similar effects on fat and skeletal muscle deposition, they have different effects on the relative growth of other tissues, especially the liver, kidneys, and other visceral organs. Different mechanisms of action could also dictate different effects or influences on nutrient requirements. This may result in differences in the response to changes in nutrient availability or to dietary manipulations.

Summary of Effects of β-Adrenergic Agonists on Growth and Composition

Chronic dietary administration of select β-adrenergic agonists markedly influences protein and lipid metabolism in farm animals, leading to marked increase in skeletal muscle protein accretion rate and, in most cases, significant reduction in lipid deposition rates. Significant improvement in carcass composition results without effect on growth of bone and with little effect on mass of visceral tissues and other organs. Improvements in growth performance appear to be greatest within the first few weeks of administration and diminish to a varying extent with continued administration. Ruminants appear to be more responsive than swine, and poultry respond least. Significant influences of diet and genotype on magnitude of response have been observed, but the nature of these interactions varies across species.

ANABOLIC STEROIDS

Naturally occurring and synthetic estrogens and androgens have been safely used to improve efficiency of growth and carcass composition of meat animals for more than 40 years. Historically, the first commercial use of an estrogen was in poultry, but this lasted only a short time. Anabolic steroids are not approved for use in growing swine in the United States; however, both estrogens and androgens are extensively used in growing cattle produced for beef. Several anabolic steroid implants are currently approved for use in beef cattle in the United States. Only one compound, zeranol, is approved for use in lambs. These approved steroid implants include the naturally occurring hormone, estradiol, the hormone progesterone in combination with estradiol or estradiol benzoate, the fungal metabolite with estrogenic properties, zeranol, the synthetic progestin, melengestrol acetate (MGA), testosterone propionate in combination with estradiol benzoate, and a synthetic testosterone analog, trenbolone acetate (TBA). Structures of estradiol, progesterone, zeranol, testosterone, TBA, and MGA are shown in Figure 2-4.

Classification of the anabolic agents previously or currently in use is based on their chemical structures and associated actions. A review of the biosynthesis and metabolism of the naturally occurring estrogens and androgens has recently been published (Hancock et al., 1991). Descriptions, approval dates, and recommended doses of the commercial products are found in papers by Schanbacher (1984), Muir (1985), and Hancock et al. (1991). Efficacy of these anabolic steroid implants is summarized in several reviews (Galbraith and Topps, 1981; Schanbacher, 1984; Muir, 1985; Roche and Quirke, 1986; Beermann, 1989; Hancock et al., 1991).

The literature on growth-performance responses to anabolic steroids indicates great variability, ranging from no

response in feedlot bulls (Richards et al., 1986) to a 69.9 percent increase in average daily gain in heifers treated with TBA (Bouffault and Willemart, 1983). Gender determines which anabolic steroid will be administered. The estrogenic compounds are generally more effective in steers. The response in females is more variable and less consistent, but the androgenic steroids are superior. 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 (Fisher et al., 1986).

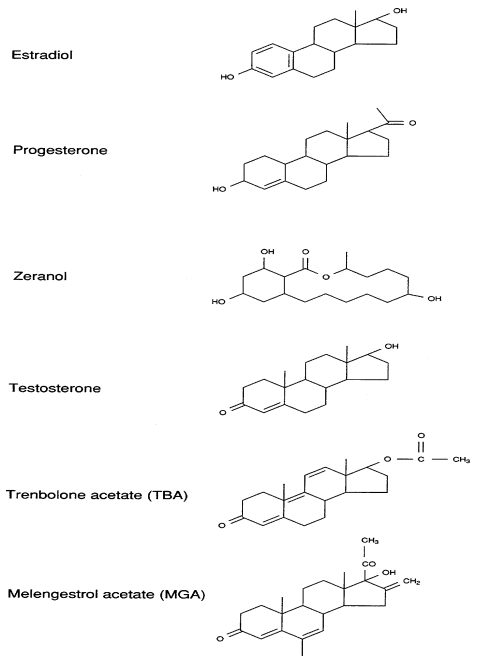

FIGURE 2-4
Chemical structures of the endogenous steroids estradiol, progesterone, and testosterone and of synthetic anabolic steroids.

Growth Performance Response to Anabolic Steroids

Rate of live-weight gain is increased 10 to 20 percent on average by anabolic steroids (Bradley et al., 1957; Sharp and Dyer, 1971; Griffiths, 1982; O'Lamhna and Roche, 1984; Gill et al., 1987; Keane and Drennan, 1987; Perry et al., 1991), but responses approaching 50 percent have been observed in lambs (Sulieman et al., 1988), steers in calorimetry chambers (Lobley et al., 1985), and steers compensating for earlier growth restriction (Keane and Drennan, 1987). It appears that young animals may respond better to steroid implants than older animals (Mader et al., 1985; Whittington, 1986; Simms et al., 1988), and this may be particularly true in bulls (Richards et al., 1986). In some studies it was observed that the rate of mass increase was higher during the early period following implantation and then decreased, which may reflect the declining circulating concentration of the anabolics after the first few weeks (Schanbacher, 1984; Lobley et al., 1985; MacVinish and Galbraith, 1988; Hayden et al., 1992).

Results from TBA-estradiol combinations appear to be superior to either implant alone. Dose-response efficacy trials involving 1,296 steers conducted for FDA approval of TBa-estradiol combinations indicate that the ADG plateaued at 118 mg TBA combined with 24 mg estradiol, but the feed efficiency plateaued at 139 mg TBA combined with 28 mg estradiol (Bartle et al., 1992). ADG was increased 18 percent and the feed: gain ratio was reduced 9.5 percent, both of which exceeded the response to 30 mg estradiol alone. Implants of 140 mg TBA alone did not improve growth performance in this and other studies (Apple et al., 1991; Hayden et al., 1992). The authors further indicated that a TBA-estradiol ratio of 5:1 is optimum for feedlot steers fed a high-grain diet. Feed conversion efficiency is usually improved with anabolic steroids, but the magnitude of the response is variable. Improvements of 5 to 14 percent have been reported (Rumsey, 1978; Greathouse et al., 1983; Mathison and Stobbs, 1983; Steen, 1985; Thonney, 1987). TBA-estradiol combinations have been shown to decrease feed: gain ratios by 10 to 13 percent (Trenkle, 1987; Eversole et al., 1989; Perry et al., 1991; Bartle et al., 1992). The degree of response to anabolic steroids is clearly influenced by dry-matter intake changes, which are also variable, and by the degree of change in composition of gain. The majority of studies in which large increases in gain were observed also showed 5 to 10 percent increases in feed intake (Thonney, 1987; Perry et al., 1991; Bartle et al., 1992) and proportional increases in lean mass in cattle (Keane and Drennan, 1987) and lambs (Sulieman et al., 1986, 1988). However, no significant changes in feed intake were observed in several studies (Griffiths,

1982; Vanderwert et al., 1985; Calkins et al., 1986; Fisher et al., 1986).

Composition of Gain

Few studies investigating the effects of anabolic steroids on growth in ruminants in the United States include direct measurement of carcass or empty-body composition, a necessity for understanding the mode of action and defining nutrient requirements. Total lean carcass (muscle) increased 9.5 and 10.4 percent in steers implanted twice with 300 mg TBA/36 mg resorcylic acid lactone over the live-weight range of 250 to 400 kg (Griffiths, 1982). Separable fat was reduced 2 percentage points ($P < 0.05$) and 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. Nitrogen balance was increased 31 and 70 percent, respectively, in two subsets of animals used in metabolism trials in this study. Nitrogen intake was not different between implanted and nonimplanted cattle, and urinary nitrogen excretion was reduced 25 and 29 percent, respectively.

Nitrogen balance of Holstein bull calves indicate that TBA-estradiol combinations increase cumulative nitrogen retention 47 percent compared with 28 percent increase in controls treated with estradiol alone (VanderWal et al., 1975). When administered separately, zeranol, progesterone, testosterone, and TBA also did not lead to a significant increase in nitrogen retention. Galbraith (1980) observed a 106 percent increase in daily nitrogen retention in beef heifers treated with a 300-mg implant of TBA for 60 days.

Long-term administration of TBA 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 (Keane and Drennan, 1987). Implanted cattle had 23.6 kg heavier side weights, 23.1 kg more lean, 3.2 kg more bone, and 2.6 kg less fat than nonimplanted cattle. Sex-by-implant interactions were not significant. Cattle implanted the longest exhibited a greater ($P < 0.05$) increase in carcass lean than cattle implanted for shorter periods. The increase in carcass weight was accounted for entirely by the increase in carcass lean observed in implanted heifers and steers, and the decrease in fat accretion was offset by increased bone growth. Dressing percentage was increased in the implanted cattle.

Choice of the experimental end point for cattle growth trials can influence the outcome and interpretation of results. Compositional differences are influenced by live weight, as dictated by normal allometric growth patterns in farm animal species. However, industry grading and pricing systems may dictate what end point is most appropriate in a commercial production system. Such is the case for fed cattle for which the degree of marbling in the longissimus muscle measured at the twelfth rib determines quality grade. 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 were compared in three breeds of steers representing different frame sizes—Holstein, Angus, and Simmental-crossbred—using rib dissection and the comparative slaughter technique at a common degree of marbling end point (Perry et al., 1991). Daily empty-body protein gain was increased 25 to 27 percent in all three breed groups with little effect on carcass composition, carcass quality grade, or retail cut distribution. However, live weight required to reach the common degree of marbling end point was increased 25 to 45 kg with the TBA-estradiol implant. Fat gain was increased by 19 percent 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 intramuscular fat concentration is achieved.

Studies using combined implants in growing and finishing lambs confirm the results observed in cattle. Lambs fed diets containing 16 percent crude protein ad libitum and implanted with TBA and estradiol-17β exhibited significant increases in intake (14 percent), live-weight gain (16 percent), and carcass lean mass (8 percent), as well as significant reductions in subcutaneous and total carcass fat (Sulieman et al., 1986). A subsequent study with similar lambs at two initial weights (24 and 37 kg) demonstrated even more substantial growth performance and carcass composition effects that were equivalent in both weight groups (Sulieman et al., 1988).

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, with lesser effects on lipid metabolism. They appear to increase feed intake in most cases.

Mechanism of Anabolic Steroid Action

Few data are available that describe the effects of anabolic steroids on protein metabolism, but even fewer data exist for assessment of direct effects of anabolic steroids on lipid metabolism in growing ruminants. Protein metabolism studies suggest that both fractional protein synthesis rate and protein degradation rate might be reduced by TBA, with the degradation rate reduced to a greater extent, resulting in an overall increased protein accretion rate in rats (Vernon and Buttery, 1976, 1978a) and lambs (Vernon and Buttery, 1978b; Sinnett-Smith et al., 1983). Combined TBA-estradiol (140 and 20 mg, respectively) implant treatment increased daily live-weight gain 50 to 60 percent at similar feed intakes and increased daily nitrogen retention 100 and 146 percent in Hereford-Holstein steers during the

first 7 weeks of treatment in a study by Lobley et al. (1985). Estimates of whole-body protein synthesis rate (based on metabolic body size) were similar throughout the 10-week experiment, while amino acid oxidation was lower in treated steers at 2 and 5 weeks. 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 most of the improvement in daily gain and nitrogen retention. Heat production was not increased in steers treated with the TBA-estradiol combination.

A recent experiment indicates that one possible mechanism responsible for TBA's ability to stimulate skeletal muscle hypertrophy may be through enhanced proliferation and differentiation of satellite cells as the result of increased sensitivity to IGF-I and fibroblast growth factor (Thompson et al., 1989).

Few data are available regarding effects of anabolic steroid implants on lipid metabolism in growing ruminants. Prior et al. (1983) demonstrated that lipogenic enzyme activity and fatty acid synthesis in vitro were elevated in subcutaneous adipose tissue from bulls implanted with estradiol. This may account for the increase in fat content of carcasses reported in some studies. St. John et al. (1987) found that TBA implants had no effect on lipogenesis in intact heifers and only tended to reduce lipogenic enzyme activities in ovariectomized heifers treated with TBA.

Assessment of indirect effects is difficult because few studies have reported determinations of circulating hormone or metabolite concentrations in animals treated with anabolic steroid implants. Treatment of lambs (MacVinish and Galbraith, 1988) or cattle (Henricks et al., 1988) with TBA and estradiol caused reduced plasma urea nitrogen concentrations, which would be expected with decreased rates of amino acid oxidation; but a causative effect has not been demonstrated. Galbraith (1980) observed no significant changes in blood hormone or metabolite levels in heifers treated with 300 mg TBA for 60 days. The review by Buttery and Sinnett-Smith (1984) notes the lack of any consistent change in ST, prolactin, insulin, or other metabolic hormones in a total of 15 studies summarized. Recent data obtained from a study in which TBA alone, estradiol alone, and TBA plus estradiol treatments were compared in yearling steers (Hayden et al., 1992) supports this conclusion.

Summary of Effects of Anabolic Steroid on Growth and Composition

The consistent net effect of anabolic steroid implant use in growing ruminants appears to be that of increasing the live weight at which carcass or empty-body fat content or concentration equals that of nonimplanted animals, thus increasing their potential mature size. Increased growth rate is usually accompanied by an increase in feed intake. Data suggest that protein metabolism is altered toward increased rates of protein synthesis and reduced rates of amino acid oxidation and/or lesser rates of protein degradation. There may be little direct effect on lipid metabolism and associated fat deposition. Indeed, as is noted by the lack of information in the literature, little is known about direct effects of anabolic steroids and combinations of same on lipid metabolism in growing ruminants.

3

Effect of Somatotropin on Nutrient Requirements of Dairy Cattle

This chapter examines the importance of nutrition in dairy cows supplemented with bovine somatotropin (bST). For background, the production response to bST is also reviewed. Evidence is presented to show that (1) nutrients required for maintenance and per unit of milk are not changed, (2) cows supplemented with bST are like genetically superior cows at the same level of milk production, and (3) cows supplemented with bST should be fed according to level of production using current National Research Council (NRC) recommendations (National Research Council, 1988b).

PRODUCTION RESPONSE

Somatotropin supplementation modifies the shape of the lactation curve (Bauman et al., 1985; Peel and Bauman, 1987). The first modification that occurs is a shift to a higher level of milk production. The second modification that can also occur is an improvement in persistency. Although responses of milk yield are fairly uniform, there is variation for individual cows within experiments and variation for groups of cows between experiments. Variation of responses may be caused by breed, parity, level of milk production, stage of lactation, and management factors such as environment, herd health, and nutritional program.

Milk Yield

Effects of bST on milk yield have been reviewed (Peel and Bauman, 1987; McBride et al., 1988; Chalupa and Galligan, 1989; Chilliard, 1989; Peel et al., 1989; Crooker and Otterby, 1991; Hartnell et al., 1991; McGuffey et al., 1991a). Examples of milk response to varying doses of bST are summarized in Chapter 2 (see Table 2-3). Similar milk responses to bST have been obtained when milking frequency was increased from 2 to 3 or 4 times per day (Armstrong et al., 1990b; Jordan et al., 1991) or when bST was administered under commercial conditions (Chalupa et al., 1988; Armstrong et al., 1990a,b; Bath et al., 1990; Duque et al., 1990; Thomas et al., 1991).

Administration of bST has involved daily injections as well as prolonged-release formulations injected at 2- to 4-week intervals. Milk response to bST varies according to stage of lactation. In general, response has been minimal when bST is administered early in the lactation cycle, prior to peak yield. Therefore, commercial use would likely involve bST treatment over the last two-thirds to three-fourths of a lactation cycle with the increase in milk yield persisting throughout this interval. Researchers have administered bST treatments for a period of a few weeks, a single lactation, or multilactations. Somatotropin has been administered for as long as eight successive lactations (see Muller, 1992).

Breed and Parity

Milk-yield responses to bST have been reported in all dairy breeds examined including African, Asian, Australian, European, North American, and South American breeds as well as Murrah buffalos. Most research has used Holstein cows, but responses of a similar magnitude have also been reported for other dairy breeds (Oldenbroek et al., 1989a,b; Duque et al., 1990; West et al., 1990a; Schams et al., 1991; Jenny et al., 1992; Pell et al., 1992).

Parity can affect the magnitude of the milk response to bST. Several researchers have demonstrated higher levels of response in multiparous cows as compared to primiparous cows when administered the same amount of bST (Baird et al., 1986; Chalupa et al., 1986; Huber et al., 1988; Palmquist, 1988; Soderholm et al., 1988; Crooker and Otterby, 1991). In contrast, other researchers have observed no difference between primiparous cows and multiparous cows in the milk response to the same dose of bST (Chalupa et al., 1988; Hard et al., 1988; Lamb et al., 1988; Samuels et al.,

1988; Bauman et al., 1989b; Franson et al., 1989; Remond et al., 1991). Hartnell et al. (1991) reported approximately 0.5 kg/day lower milk-yield response but a similar percent response to various doses of bST in primiparous cows as compared to multiparous cows. On the basis of 15 on-farm trials in the United States, Thomas et al. (1991) reported that responses in milk production for multiparous cows were higher than responses of primiparous cows at all stages of the lactation cycle. The observed variation in milk response between primiparous and multiparous cows is likely related to differences in level of production, differences in the shape of the lactation curve, and/or differences in the extent to which primiparous cows need to divert nutrients for growth in order to achieve mature size.

Management and Genotype

Quality of management will be the major factor affecting the magnitude of milk response to bST (Bauman, 1987). Responses do vary on a per-herd basis according to average pretreatment production when pretreatment differences are related to quality of management (Chilliard, 1989; Peel et al., 1989; Crooker and Otterby, 1991; Bauman, 1992). Several studies have examined the relationship between genotype and milk response to bST. With one exception (Michel et al., 1990), results demonstrate that there is no evidence of a genotype-response interaction in bST-supplemented cows (McDaniel and Hayes, 1988; Gravert, 1989; Leitch et al., 1990; Nytes et al., 1990).

Within a herd, where differences in quality of management are less of a factor, studies with bST have consistently shown that the variation within bST-supplemented groups is similar to that of untreated groups (Peel et al., 1989; Bauman, 1992). In addition, the level of response to bST appears to be similar for individual cows regardless of whether they were high- or low-level milk producers in the herd prior to initiation of bST supplementation (Peel et al., 1989; Thomas et al., 1991). Thus, to a large extent, all cows in a herd respond to bST in a fairly similar manner.

Environment

Cows exposed to hot or cold environments have production responses to bST similar to cows in a thermoneutral environment. In the Climatology Laboratory at the University of Missouri, cows were subjected to thermoneutral (15 to 22° C), hot (25 to 35°C), and cold (-5 to 5°C) daily cycles of temperature (Becker et al., 1990; Johnson et al., 1991; Manalu et al., 1991). Under all cycles, cows supplemented with bST produced more heat, as expected from the higher milk yield; but dissipation of heat also increased so that no adverse heat balance problems occurred. In other short-term studies in Arizona (Armstrong et al., 1990b), Florida (Elvinger et al., 1988, 1992; Staples et al., 1988; Zoa-Mboe et al., 1989), Missouri (Mohammed and Johnson, 1985), and Southern California (Chalupa et al., 1988) and in long-term studies in Arizona (Huber et al., 1990) and Georgia (West et al., 1990b, 1991), heat-stressed cows responded positively to exogenous bST. However, magnitude of milk responses to bST under differing environmental conditions may depend largely on the effect of environment on feed intake. Similar to untreated cows, nutritional interventions such as additional water, dietary potassium, and the use of low-heat increment feeds like fat should be considered during periods of high temperature and humidity (Beede and Collier, 1986).

Milk Composition

Concentration of fat and protein in milk is normally variable because of factors such as genetics, stage of lactation, age, diet composition, nutritional status, environment, and season (Linn, 1988; Sutton, 1989). These factors also affect the milk composition of bST-supplemented cows, and the variations in content of fat and protein are of the same magnitude as that usually observed in dairy herds. The effect of bST on milk fat and protein composition depends on the nutritional status of the cows both before and during bST treatment (Peel and Bauman, 1987; McBride et al., 1988; Bauman et al., 1989a; Chalupa and Galligan, 1989; van den Berg, 1989, 1991; Dell'Orto and Savoini, 1991; Barbano et al., 1992; Laurent et al., 1992; Lynch et al., 1992). In the early stages of bST treatment, increases in milk fat and decreases in milk protein may occur whenever milk-yield increases cause changes in energy and protein balance in the cow such that body fat and protein stores are mobilized to meet the increased nutrient demands. These changes in energy balance are similar to, but smaller than, changes that normally occur at the onset of lactation. With prolonged bST administration, cows adjust their voluntary feed intake to meet their increased nutrient requirements, and nutrient balance is restored. In general, the percentages of milk fat and protein were not different for bST and control cows when bST was administered over a full lactation (see reviews cited above). Overall, the results demonstrate that nutritional status affects the fat and protein composition of milk and that this relationship is not altered with bST supplementation.

Generally, the proportion of total milk protein represented by whey proteins and casein, and the composition of casein (α-casein, *β*-casein, κ-casein) are not altered by bST supplementation (Baer et al., 1989; Leonard et al., 1990b; Austin et al., 1991; van den Berg, 1991; Barbano et al., 1992; Laurent et al., 1992). Because protein and nonprotein nitrogen (NPN) content of milk reflect protein adequacy of diets (Refsdale et al., 1985), variations caused by bST supplementation will depend on protein nutritional status regardless of whether the animal receives exogenous bST.

Milk from cows supplemented with bST did not differ in content of vitamin A, thiamin, riboflavin, pyridoxine, vitamin

B_{12}, pantothenic acid, or choline; content of biotin was increased slightly (van den Berg, 1989, 1991; Kirchgessner et al., 1991b).

Milk concentrations of nutritionally important mineral elements (calcium, phosphorus, sodium, iron, copper, and manganese) were not affected by bST (Eppard et al., 1985, 1991; Annexstad et al., 1990; van den Berg, 1991). Other studies have also observed normal milk concentrations of ash, calcium, and phosphorus throughout lactation in bST-supplemented cows (Hard et al., 1988; Bauman et al., 1989b; Oldenbroek et al., 1989a,b; Pikus et al., 1989; Hartnell et al., 1991).

Feed Intake

Production responses to bST have been obtained under a wide variety of feeding programs including feeding total mixed rations, feeding grain and forage separately, and pasture-fed cows. A particularly important adaptation is that cows typically adjust their voluntary feed intake upward within a few weeks after initiation of bST treatment (Peel and Bauman, 1987; Chalupa and Galligan, 1989; Chilliard, 1989). Bauman et al. (1985) suggested that feed intake regulation was more likely associated with tissue metabolism and use of nutrients than with bST per se. Indeed, covariate adjustment for the increased production of fat-corrected milk showed that most of the increased consumption was accounted for by higher milk yields (Marsh et al., 1988). In addition, energy status of the animal, level of nutrient intake at the onset of bST treatment, and the magnitude and pattern of the milk response all are important factors driving dry-matter intake. Current equations used to estimate feed intake can be applied to cows supplemented with bST (National Research Council, 1987, 1988b).

In some long-term bST studies, dry-matter intake (energy intake) was reported to be similar to that of control cows. However, in some of these studies, bST was administered once every 28 days and dry-matter intake was numerically increased in a dose-dependent manner (Leonard et al., 1990a; McGuffey et al., 1991a,b). Because voluntary intake did not increase to an extent that matched the increased milk yield, body weight gain was significantly less and body condition scores were substantially lower (approximately 0.5 points) at the end of lactation in the bST-treated cow. Only during the second lactation (Leonard et al., 1990a) was the increase in dry-matter intake significant ($P < 0.05$) and body weight gain and body condition scores similar among treatment groups. Leonard et al. (1990a) postulated that when cows are treated with a prolonged-release formulation of bST, during which milk production returns to baseline and remains at that level for a period of time before bST readministration, weaker signals are sent to drive voluntary intake.

Attention to management factors that affect dry-matter intake will become important in maximizing the milk response to bST. Excellent quality forage is a critical component in obtaining high levels of voluntary intake. Other important factors include adequate bunk space, ease of access to the feed bunk, ad libitum and frequent offerings of feed, unlimited access to clean water, nutritionally balanced diet, adequate dietary protein, proper levels of effective as well as digestible fiber, and control of temperature and humidity. Even though cows adjust their feed intake upward within a few weeks after initiation of treatment, the magnitude of response to bST likely will depend on nutrients provided by feeding programs. If cows consume an insufficient quantity of nutrients or are fed diets with inadequate nutrient balances, the response to bST will undoubtedly decrease according to the extent of the inadequacy (Bauman, 1992).

NUTRIENT REQUIREMENTS

More nutrients are needed for the increased synthesis of milk and milk components that occurs with bST supplementation of lactating dairy cows. Initially, body stores of protein and fat may provide additional nutrients, but nutrients for sustained increases in production are derived from changes in voluntary intake (see previous section) and the coordinated changes in the metabolism of body tissues so that more nutrients can be used for milk synthesis (Bauman and McCutcheon, 1986; Bauman et al., 1989a; Vernon, 1989; Breier et al., 1991). The mechanism of action for bST and effects on specific metabolic processes are detailed in Chapter 2 (see Table 2-4). Overall, it is these orchestrated changes that allow the animal to achieve an increased milk yield while remaining normal and healthy. In most regards, the bST-treated cow is similar to the genetically superior cow with a comparable milk production (Table 3-1). The following sections will address the effect of bST on requirements for specific nutrients and on recommendations for diet formulation and feeding programs.

Energy

A lactating cow requires a substantial quantity of energy to meet its requirements for maintenance and milk production. Therefore, formulating diets that allow for an adequate energy intake (rumen digestible carbohydrate) is a major consideration. Body fat reserves can provide a temporary supply of energy and these are typically important in early lactation. In a high producing dairy cow, the use of body energy reserves in the first month of lactation can be energetically equivalent to about one-third of the milk produced (Bauman and Currie, 1980). However, over a lactation cycle these body fat reserves must be replenished in preparation for the next lactation.

The effects of bST on dimensions of energy metabolism of dairy cows have been examined. Studies have consistently

demonstrated that bST treatment does not alter the digestibility of dietary dry matter, energy, or carbon (Peel et al., 1981, 1985; Tyrrell et al., 1988; Sechen et al., 1989a; Kim et al., 1991; Kirchgessner et al., 1991a; Lynch et al., 1991; Robinson et al., 1991).

TABLE 3-1 Comparison of Bovine Somatotropin (bST)-Treated to Genetically Superior Cows Producing the Same Quantity of Milk

Variable	Genetically Superior	bST-Treated
Feed intake	Higher intake; intake increases after parturition	Intake increases to match higher milk yields
Digestibility of feed	No differences[a]	No differences[a]
Maintenance	No differences[a]	No differences[a]
Partial efficiency of milk synthesis	No differences[a]	No differences[a]
Mammary glands	More secretory tissue; activity per cell not known	Better maintenance of secretory cells and/or higher synthetic rate per cell
Body reserves	Greater use in early lactation	Increased use during first weeks of bST
Efficiency	Increased; larger portion of nutrients used for milk synthesis	Increased; larger portion of nutrients used for milk synthesis

[a] No differences are apparent with precision of current methodology.
Source: Adapted from Peel and Bauman (1987).

Bioenergy studies demonstrate that the energy requirements for maintenance and milk production are not altered in bST-treated cows (Tyrrell et al., 1988; Sechen et al., 1989a; Kirchgessner et al., 1991a). These calorimetry measurements have involved bST administration for short-term and long-term periods and included animals in both positive and negative energy and nitrogen balances. Results indicate that heat loss in bST-treated cows was predictable from changes in milk yield and nutritional status. When cows were in negative energy balance, bST caused an increased heat energy loss equal to that predicted for the increased milk yield (Tyrrell et al., 1988; Kirchgessner et al., 1991a). In contrast, when energy balance was positive, supplementation with bST had no effect on energy lost as heat because the increase in heat associated with the extra milk matched the decrease in heat associated with the reduction in synthesis of body fat (Sechen et al., 1989a).

For bST-treated cows, theoretical calculations of energy metabolism are also in agreement with observed changes. This close agreement would only occur if digestibilities and the energy requirements for maintenance and milk are unchanged. These comparisons have included studies in which changes in body composition and energy balance were compared to theoretical estimates (e.g., Soderholm et al., 1988; Brown et al., 1989; Chilliard et al., 1991; McGuffey et al., 1991b; McGuffey and Wilkinson, 1991), studies in which kinetic measurements of metabolite turnover were compared to energy balance (Bauman et al., 1988), and long-term studies in which theoretical and observed estimates of energy efficiency were compared (e.g., Bauman et al., 1985, 1989b; Soderholm et al., 1988).

Overall, results demonstrate that the current NRC requirements (National Research Council, 1988b) for maintenance and milk production are appropriate for cows receiving bST (Table 3-1). The bST-treated cows have a greater total energy requirement because they are producing more milk. However, they have greater productive efficiency (milk/unit of feed; Chapter 2) because maintenance is unchanged and a greater proportion of total nutrient intake is being used for milk synthesis (Table 3-1). This is frequently referred to as a dilution of maintenance effect and is also the basis for gains in efficiency achieved with other dairy technologies (Bauman, 1992).

Protein

Absorption of essential amino acids from digested protein is vital for maintenance, growth, reproduction, and lactation of dairy cattle. These amino acids are derived either from microbial protein produced during fermentation of feed in the rumen or from dietary protein that escapes rumen fermentation. An additional short-term supply of amino acids may be derived from the mobilization of labile tissue protein, and use of these reserves would typically occur in early lactation. Estimates of the protein reserves available to support milk synthesis indicate they are quantitatively limited (National Research Council, 1988b).

The ruminal production of bacterial and protozoal crude protein is a function of energy intake (rumen digestible carbohydrate) (National Research Council, 1985). In addition, an adequate supply of nitrogen from degradable protein and nonprotein nitrogen (NPN) is essential to maximize feed intake, ruminal digestibility, and microbial protein yield (National Research Council, 1988b).

The protein in practical dairy forage and concentrate sources supplies some dietary protein that escapes rumen fermentation, and this protein plus the microbial protein

produced from the degraded protein and NPN in these feeds may be enough to produce 20 kg milk/day (Conrad and Hibbs, 1968; Tamminga and von Hellemond, 1977). As milk production increases, a substantial amount of additional dietary protein from protein supplements must escape rumen fermentation to meet the cow's requirement for protein. The current recommendations for protein requirements of lactating cows include both a percentage of rumen degraded protein, to allow for maximum microbial growth and digestion of fiber, and a percentage of undegradable protein that will escape ruminal degradation and augment the supply of essential amino acids that can be absorbed from the small intestine (National Research Council, 1988b).

Long-term studies (one or more lactations) have demonstrated that by following current recommendations, bST-supplemented cows produce milk with normal protein content and composition (see previous sections). In addition, changes in protein supply to bST-treated cows alter protein balance and milk protein content in an identical manner as occurs in untreated cows, as previously discussed. Therefore, the results from these extensive studies are consistent with the protein requirements for maintenance and milk production being the same for cows receiving bST supplementation. The possibility of an increase in biological value, such as that which occurs with ST treatment of growing pigs (Chapter 5) and growing ruminants (Chapter 4), has not been examined for lactating cows. If such an effect occurred it would represent a subtle decrease in the protein requirements. However, with current feeding systems for dairy cows, the precision of estimates of the supply and requirement for protein (amino acids) makes it difficult to experimentally detect or commercially implement subtle differences in biological value of absorbed amino acids (Clark et al., 1992).

Several studies have examined aspects of protein metabolism in cows treated with bST. Overall, the digestibility of dietary protein is not altered in cows treated with bST (Peel et al., 1981, 1985; Tyrrell et al., 1988; Sechen et al., 1989a; Kim et al., 1991; Lynch et al., 1991; Robinson et al., 1991; Winsryg et al., 1991a,b).

de Boer and Kennelly (1989) found an increased milk yield response to bST when cows were fed diets containing 16 versus 11 percent crude protein. A subsequent report by de Boer et al. (1991) observed no difference in bST response for cows fed diets containing 17 versus 24 percent crude protein, although results were confounded by the fact that bST-treated cows produced no more milk than untreated cows. McGuffey et al. (1990) examined protein level and undegradability of protein for bST-treated cows and found that both higher protein level and increased undegradability of protein enhanced response to supplemental bST. However, these results were confounded by the energy sources of the diets, so that response could have been caused by energy (carbohydrate) source rather than protein. Performance differences may also be related to dietary differences in the quantity and quality of absorbed amino acids. Other studies comparing protein sources of different degradabilities indicated that level of rumen undegradable protein had no effect on the response to supplemental bST (Lormore et al., 1990; Hof et al., 1991; Winsryg et al., 1991b; Calsamiglia et al., 1992). In addition, postruminal infusion of casein (Peel et al., 1982) or essential amino acids (Aldrich et al., 1990; Lynch et al., 1991) did not alter response of cows to exogenous bST.

Data currently available indicate that dietary recommendations for quantity of protein and proportions of rumen degradable and undegradable protein (National Research Council, 1988b) are adequate to meet the needs of cows supplemented with bST. Therefore, protein requirements of the bST-treated cows are identical to the untreated cow producing the same quantity of milk.

Vitamins and Minerals

There have been no studies that specifically examined the effects of bST supplementation on the vitamin and mineral requirements of lactating cows. Studies involving bST supplementation for weeks or months as well as those involving treatment for one or more lactations have simply followed current dietary recommendations for vitamins and minerals. If these recommendations were inadequate, one should see abnormalities in health and performance and classical subclinical and clinical symptoms of vitamin and mineral deficiencies or excesses. No study has reported observing such abnormalities or symptoms. Rather, studies with bST-supplemented cows have consistently documented increases in milk yield and treatment has had no effect on milk content of vitamins and minerals (see previous sections). Even when pharmacologic doses of bST were used (up to 3 g/14 days), milk concentrations of ash, calcium, phosphorus, magnesium, and zinc remained normal and there were no bone abnormalities as evidenced by a range of radiological, macroscopic, and microscopic indices (Eppard et al., 1991). This total pattern of mineral homeostasis is consistent with the concept that bST coordinates mineral partitioning (Peel and Bauman, 1987; Bauman et al., 1989a). Overall, results demonstrate that mineral and vitamin requirements must be similar between bST-supplemented cows and untreated cows of comparable production and indicate that requirements are adequately met by following current recommendations.

Fiber

In general, the fiber content of the diet of dairy cattle is inversely related to its net energy content. Nevertheless, a minimum amount of fiber of the proper quality and physical form is necessary to obtain maximum dry-matter and energy

intake, maintain adequate ruminal fermentation, and allow for normal performance and health of the lactating cow. The amount of fiber to be included in the diet of dairy cattle is influenced by a number of variables such as the animal's level of production, the type of fiber, the particle size and distribution of the fiber, buffering capacity of the forage, and frequency of feeding. Animals producing large amounts of milk should receive more energy and less fiber than cows producing smaller amounts (National Research Council, 1988b).

Current NRC recommendations are that a minimum of 21 percent acid detergent fiber (ADF) and 28 percent neutral detergent fiber (NDF) be provided to cows during the first 3 weeks of lactation (National Research Council, 1988b). During times of high milk production, however, ADF and NDF contents of the diet may be reduced to 19 and 25 percent, respectively, so that adequate energy can be included to meet the cow's requirements. Virtually all the long-term studies have followed these recommendations for both control and bST-treatment groups and none have highlighted any unusual observations that might be related to rumen fermentation. Therefore, it appears that current recommendations apply for dietary fiber, even if cows are receiving supplemental bST. This is not surprising because the biological effects of bST are associated with the utilization of absorbed nutrients rather than digestive processes (Chapter 2).

Energy Density

As the level of milk production and genetic merit for milk yield increase, the energy intake of dairy cows must also increase. Energy intake is affected by energy density of the diet and factors affecting dry-matter intake. Three ways to increase the energy density of the diet are (1) increase the proportion of concentrate versus forage in the diet, (2) select concentrate ingredients of higher energy content (i.e., shelled corn versus ear corn or oats; soy hulls versus oat hulls), or (3) add fat sources such as animal fat, vegetable oils, oil seeds, or inert/bypass fat sources. The maximum amount of concentrate that can be used without causing milk fat depression and disturbances in digestion, metabolism, and production depends on the type of forage used as well as its physical form. Generally, higher proportions of concentrate can be used without the need for dietary buffers to maintain milk fat content when the major forage is alfalfa or grass hay, haylage, or silage as compared to corn or small grain silages (Erdman, 1988; National Research Council, 1988b). However, minimum levels of fiber should be maintained (National Research Council, 1988b). Under some circumstances, supplementation with dietary buffers has increased dry-matter intake and milk yield. The most significant improvements from feeding buffers have been obtained in early stages of lactation when corn silage was the major forage fed (National Research Council, 1988b). Chalupa et al. (1984, 1985), feeding corn silage as the only forage (40 percent of dietary dry matter), reported milk yield responses of bST-treated cows to be additive to responses with sodium bicarbonate.

Altering the forage-concentrate ratio affects the lactational performance of dairy cows. Because of gut-fill limitations with high forage diets, increasing the proportion of concentrates results in a greater energy intake thereby allowing for a higher level of milk production. Recently, Tessmann et al. (1991b) reexamined forage-concentrate ratios using alfalfa silage as the forage source and cows of high genetic potential for milk yield. Consistent with earlier work (National Research Council, 1987), they observed that a modest decrease in milk yield occurred as the proportion of forage in the diet was increased. Tessmann et al. (1991b) also demonstrated that replenishment of body reserves was less adequate as the dietary ratio of forage-concentrate was increased; these results are consistent with earlier work and the fact that their design based the dietary shifts on stage of lactation rather than level of milk yield or body condition scores.

Tessmann et al. (1991a) also examined the effects of bST treatment over the interval of 13 to 43 weeks postpartum using two of these dietary groups. Although milk yield was lower in the control group receiving the higher proportion of forage as compared to the low-forage control group, cows on both diets responded in 3.5 percent fat-corrected milk to a similar extent with bST treatment. Consistent with their design and the work of others, effects on replenishment of body reserves were as expected, regardless of whether animals received bST.

The impact of variations in the forage-concentrate ratio on milk response to bST has also been examined by others. Forage-concentrate ratios over the range of 60:40 to 40:60 had no effect on the lactational response to bST (Hemken et al., 1988; McGuffey et al., 1991b). In fact, typical increases in milk yield have also been observed even when pasture was the only source of nutrients (Peel et al., 1985; McCutcheon et al., 1989).

Selecting fiber and carbohydrate sources with higher energy densities is another way of increasing energy intake. Beet and citrus pulp and soy hulls are highly digestible fiber sources containing twice as much energy as oat hulls and 10 times as much energy as rice hulls (National Research Council, 1988b). Corn grain contains more energy than ear corn, oats, or milo. Although corn contains more energy than barley, the barley starch has been reported to be more digestible. Eisenbeisz et al. (1990) reported that cows fed corn-based diets achieved greater milk production than cows fed barley-based diets; however, the milk response to bST was similar.

Substitution of supplemented fat for a portion of the starch and cereal grains in the diets of high-producing cows is a way of maintaining high energy intakes and high fiber intakes (see reviews by Palmquist and Jenkins, 1980; Coppock and Wilks, 1991). In some situations, addition of fat to

the diet has been shown to impair ruminal fermentation, decrease fiber digestibility, and lower milk content of fat and protein. However, these effects are related to the level and type of fat supplement. Animal fats, blended animal-vegetable fats, or oilseeds are preferred over vegetable oils (National Research Council, 1988b). The level of added fat typically should not exceed 0.5 to 0.7 kg/day or 4 to 5 percent of the total mixed diet on a dry-matter basis; however, the use of ruminally inert fats may allow inclusion of slightly higher levels in the diet.

A few investigators have examined the effect of adding supplemental fat to the diet of cows treated with bST. Their studies demonstrated that supplemental fat in the corn-based and barley-based diets, both ruminally active fat (Lough et al., 1988) and ruminally inert fat (Lormore et al., 1990; Marty and Block, 1990), had no effect on milk response of bST-treated cows over and above that of bST-treated cows fed a diet without added fat. In a study by Schneider et al. (1990), there was a tendency for ruminally inert fat to enhance the galactopoietic effect of bST, but results were not significant. Therefore, results indicate the energy density required in diets for cows of a given milk yield should be similar, independent of bST administration.

Body Condition

Although body stores of protein and fat may be needed to provide additional nutrients until feed intake is adjusted upward, Peel et al. (1989) reported that body condition score at the start of bST supplementation was not associated with the magnitude of response. In contrast, Crooker and Otterby (1991) reported a major effect of body condition prior to start of bST supplementation on milk response to bST. Achieving proper body condition prior to calving should be an important management strategy.

Lower body fat in cows supplemented with bST (Bauman et al., 1988; Soderholm et al., 1988; Brown et al., 1989; Chilliard et al., 1991; McGuffey et al., 1991b) is the result of partitioning calories to milk production at the expense of body fat. It therefore is important to monitor body condition so that body reserves can be replenished during late lactation or the dry period. Impact of bST on body composition and body condition score depends on the magnitude of the milk response to bST and the level of intake and nutrient density of the diet.

Movement of cows to feeding programs with lower nutrient densities should be on the basis of milk yield and body condition. Restoration of body condition is more efficient in late lactation than during the dry period; however, if cows are not in proper body condition at dry-off, then dry cow management should be aimed at replenishing reserves prior to calving. Economics and management strategies may indicate that with higher levels of milk production and changes in persistency obtained with the use of bST, longer calving intervals may be appropriate. This strategy would provide the additional time in late lactation needed to replenish body reserves for subsequent lactations (Crooker and Otterby, 1991; Bauman, 1992; Patton and Heald, 1992).

SUMMARY

The physiology and metabolism of bST-treated cows are like those of genetically superior cows at the same level of production. Substantial responses in milk yield occur when bST is administered over the last three-fourths of lactation. Lactation curves are shifted upward and are generally more persistent. Dairy cattle of all breeds and all parities respond to exogenous bST administration. Milk composition remains normal in bST-supplemented cows and factors that affect milk composition, such as nutritional status, genetics, and stage of lactation, cause the same variation as observed for untreated cows. St administration does not alter digestibility of the dietary nutrients, maintenance requirements, or the partial efficiency of milk synthesis. Thus, current NRC recommendations for nutrient requirements should be followed for bST-supplemented cows. Similarly, the NRC recommendations for diet formulation and feeding programs are the same as for cows administered bST. These include such considerations as dietary levels of fiber, energy density, and degradable and undegradable protein as well as nutritional considerations in regard to maintaining adequate body reserves. Overall, the nutritional needs and feeding strategies for cows supplemented with bST are identical to current recommendations for untreated cows of comparable milk production.

4

Effect of Metabolic Modifiers on Nutrient Requirements of Growing Ruminants

Rate and efficiency of nutrient use for growth are adversely affected when availability of essential nutrients (protein, vitamins, and minerals) and energy intake are not adequate. Nutrient requirements in growing ruminants have traditionally been empirically determined by altering diets or intake to define nutrient levels at which growth performance responses are maximized. Nutrient requirements are influenced by digestibility of feedstuffs, maintenance requirements, composition of gain, and metabolic processes that affect the efficiency of nutrient use. Energy and amino acid requirements for nonruminants can be estimated from known or measured rates of protein and amino acid deposition plus estimates of endogenous use (i.e., amino acid oxidation) for the whole body. When energy intake is adequate, whole-body protein accretion rates increase linearly with a stepwise increase in dietary protein intake until a plateau is achieved. That level of intake which produces the maximal response can be used as an estimate of the animal's requirement. The same principle applies for estimating energy intake requirements when protein intake is adequate. Excess energy intake results in increased lipid deposition, which causes decreased efficiency of feed conversion.

The complexity of the ruminant digestive system, particularly the contribution of the rumen microflora to nutrient absorption in the lower tract, makes it difficult to clearly define how well diets or diet formulations meet nutrient requirements in the growing animal. This complexity is responsible for the use of protein requirements for growing ruminants rather than use of individual amino acid requirements, as have been defined for nonruminants. The pattern of amino acids available for absorption in the small intestine can be predicted with reasonable accuracy in nonruminants. However, in ruminants, amino acids entering the small intestine come from rumen microbial protein, dietary protein that has escaped rumen fermentation, and endogenous secretions or contributions. Therefore, it is difficult to estimate both the quantity and profile of individual amino acids available for absorption from the small intestine of ruminants and the impact of amino acid nutriture on growth under normal management systems.

The effects of metabolic modifiers such as somatotropin (ST) and β-agonists on protein (amino acid) and energy use are primarily postabsorptive. Metabolic modifiers alter metabolism so that a greater proportion of absorbed nutrients is used for protein synthesis and deposition. Although ST, β-agonists, and anabolic steroids all improve rates of skeletal muscle growth, they differ in their metabolic effects on protein, lipid, and carbohydrate metabolism. They also differ in whether they increase organ and bone growth. This necessitates independent investigations into the effects of ST, β-agonists, and anabolic steroids on the nutrient requirements of growing ruminants. Information that defines mechanism(s) of action for each metabolic modifier is valuable in designing experiments or building models for predicting nutrient requirements in growing ruminants administered ST, growth hormone-releasing factor (GRF), a β-adrenergic agonist, or anabolic steroid implants. These mechanisms have been discussed in preceding chapters of this report. Only two recent reviews have addressed the issue of whether nutrient requirements are altered in livestock that have been administered metabolic modifiers (Boyd et al., 1991; Reeds and Mersmann, 1991). The effects of anabolic steroids in cattle were not addressed in these reports and a considerable amount of additional information has been produced since these reports were published. The objective of this chapter is to summarize what is known regarding the potential impact of the chronic administration of ST, GRF, select β-adrenergic agonists, or anabolic steroids on nutrient requirements of growing ruminants.

EFFECTS OF SOMATOTROPIN OR GROWTH HORMONE-RELEASING FACTOR

Effects of exogenous ST or GRF on nutrient requirements must be evaluated to determine whether feeding strategies should be changed to maximize response. Administration of GRF is an alternative approach to direct administration

of ST for elevating circulating levels of ST through stimulating endogenous ST secretion. It appears that the biology of ST effects on variables influencing nutrient requirements is similar in ruminants and swine, but data on nutrient requirements are limited for ruminants and more extensive for growing pigs (see Chapter 5).

Relative and absolute rates of energy and protein intake influence composition of gain. Therefore, effects of ST on energy or protein metabolism could influence nutrient requirements. Black and Griffiths (1975) clearly demonstrated relationships between energy and protein intake on nitrogen balance in untreated cross-bred lambs, ranging in weight from 3 to 38 kg and fed only milk to assess the tissue growth requirements independent of rumen microbial protein contributions. They observed that when nitrogen intake was inadequate, nitrogen balance was independent of energy intake but linearly related to absorbed nitrogen and metabolic body weight. When nitrogen intake was in excess of requirement, nitrogen balance increased linearly with metabolizable energy (ME) intake at a rate that decreased with increasing live weight. They also demonstrated that when nitrogen requirement was expressed per unit of energy intake, it was found to be constant for all lambs irrespective of live weight when intake was 55 kcal/kg^{75} (near maintenance of body protein). As ME per unit metabolic body weight (BW^{75}) was increased above this level, nitrogen requirement per unit ME increased for lambs weighing less than 23 kg and decreased for heavier lambs. Determining the effects of ST on nutrient requirements of growing ruminants requires integration of these principles and estimating contributions of rumen microbial protein and volatile fatty acids to tissue amino acid and energy requirements.

Effects of bST in Growing Cattle

The effects of exogenous administration of ST in growing ruminants have recently been summarized (Enright, 1989; Beermann and DeVol, 1991; McBride and Moseley, 1991; Moseley et al., 1992). Data from 21 trials with growing cattle indicate that with moderate doses of bST, average daily gain (ADG) is increased 10 to 15 percent and feed conversion efficiency is improved 9 to 20 percent, while carcass lean (muscle) content is increased 5 to 10 percent and carcass fat content is reduced 10 to 15 percent. These averages of responses are weighted toward greater emphasis on the longer-term studies in which growth performance of control animals has been shown to be not unusually low and represent summaries of data published as abstracts, in some instances. The responses to different doses of ST that reflect representative data for variation in initial weight, treatment time, frequency of administration, sex, breed, and diet are presented in Table 4-1.

The studies in which much larger increases in ADG or feed conversion efficiency were observed are those in which short-term administration periods of 8 to 21 days were utilized (Wolfrom and Ivy, 1985; Hancock and Preston, 1990) or those in which rates of gain of untreated cattle were less than 0.3 kg/day (Peters, 1986; Hancock and Preston, 1990). It is necessary to note that low ADG in the study by Peters was imposed as a restricted feed-intake aspect of the experimental design and that high doses of ST may impair weight gain because of the greater reduction of lipid accretion rate that occurs and associated effects on feed intake (Moseley et al., 1992).

Dose-response data that provide the needed information for assessing changes in nutrient requirements in growing cattle are limited. Nitrogen retention was increased and plasma urea nitrogen decreased in a dose-dependent manner in growing Holstein heifers administered 0, 6.7, 33, 67, 100, and 200 µg bST/kg live weight/day (Crooker et al., 1990). The maximum increase of 23 percent was observed at the highest dose, but the curvilinear relationship suggests that a dose between 50 and 100 µg/kg live weight achieves nearly maximal response. This is in agreement with data from dose-response studies with bST in lactating cows and porcine ST (pST) in growing pigs. Digestibility of dry matter and nitrogen were not affected by bST treatment.

More recent published results of dose-titration experiments in which recombinant bST was administered to finishing steers by injection (Moseley et al., 1992) or implant (Dalke et al., 1992) demonstrated a linear dose-dependent reduction in dry-matter intake and feed/gain. Carcass protein was increased and carcass lipid decreased without altering dressing percentage. Although high-concentrate diets with protein levels in excess of NRC requirements were fed, information was not available to indicate whether either energy or protein intake might have constrained the growth response, particularly at the highest doses administered. Addition of rumen escape protein (0.76 percent) did not enhance growth performance or carcass protein content in the implant study.

Summary of the data implies that dry-matter intake is decreased with ST administration in finishing cattle fed high-concentrate diets. Unfortunately, no definitive data are available for titration of energy or protein intake requirements in ST- or GRF-treated cattle. Results from at least three studies (Eisemann et al., 1986a,b; Peters, 1986) indicate that ST treatment of cattle fed slightly above maintenance levels of energy intake results in conservation of body protein or amino acids to support increases in nitrogen retention or carcass lean accretion. Eisemann et al. (1986a) observed significantly reduced leucine oxidation and a 6 percent increase in fractional protein synthesis rate in heifers administered ST for 14 days. Subsequently, Eisemann et al. (1989b) found that rates of radio labeled leucine incorporation into protein tended to increase and that whole-body rates of leucine oxidation were reduced in rapidly growing steers administered exogenous bST. Furthermore, it was

noted that bST increased (approximately 50 percent) the incremental efficiency of protein deposition. Total energy balance and total heat production were not altered by ST, indicating that gross efficiency of utilization of ME for gain was not changed (Eisemann et al., 1986b).

TABLE 4-1 Representative Data of the Effects of Somatotropin (ST) on Growth Performance and Composition of Cattle and Lambs

Treatment/Dose	Average Daily Gain (%)	Feed:Gain (%)	Carcass Protein (%)	Carcass Fat (%)	Reference
			Cattle		
bST 75 µg/kg/day sc	None	ND	22.4[a]	–32.3[a]	Peters, 1986
bST 600 µg/kg/day sc	8.6	–2.0	0[c]	–17.0[c]	Sandles and Peel, 1987
bST 25 µg/kg/day sc	7.1	–3.8	ND	ND	Kirchgessner et al., 1987
bST 50 µg/kg/day sc	8.3	–5.7	ND	ND	
bST 100 µg/kg/day sc	10.8	–7.0	ND	ND	
bST 33 µg/kg/day sc	7.9	–12.1	10.6[b]	–13.4[b]	Moseley et al., 1992
bST 100 µg/kg/day sc	–7.0	–6.8	13.6	–21.2	
bST 40 mg/wk implant	–1.7	–4.7	5.3[b]	–5.3[b]	Dalke et al., 1992
bST 80 mg/wk implant	1.7	–5.6	4.7	–9.2	
bST 160 mg/wk implant	5.3	–12.1	9.4	–11.8	
			Lambs		
oST 375 µg/kg/day sc	20	–14	25.0[c]	–36.0[c]	Wagner and Veenhuizen, 1978
bST 25 µg/kg/day sc	3.1	–3.0	8.4[d]	–01.8[d]	Johnsson et al., 1987
bST 100 µg/kg/day sc	–4.3	0	9.3	–16.5	
bST 250 µg/kg/day sc	1.3	–7.2	11.4	–25.2	
bST 50 µg/kg/day sc	20.0	–13.0	10.0[e]	–00[e]	Zainur et al., 1989
bST 150 µg/kg/day sc	32.0	–18.0	13.0	–10.1	
bST 250 µg/kg/day sc	45.0	–29.0	16.0	–21.3	
oST 40 µg/kg 4 times daily sc	12.0	–22.0	36.0[c]	–30.0[c]	Beermann et al., 1990

NOTE: Percent (%) indicates gain above controls. ND, not determined.

[a]Chemical composition of rib dissection tissues.
[b]Daily nitrogen retention response.
[c]Chemical composition of carcass gain expressed in g/day.
[d]Physical dissection of the neck and shoulder joint.
[e]Chemical composition of the carcass.

A small increase in net energy requirement is probable for maintenance in bST-treated cattle because significant increases in weights of the liver, kidneys, skeletal muscle, and bone have been observed, although heat production data do not support this. Increased efficiency of use of absorbed amino acids for protein gain may have been responsible for the significant increases in nitrogen retention or protein gain observed in these and other studies, the magnitude of which is less than that observed in growing and finishing pigs treated with similar doses of ST.

Direct comparisons of several protein intake levels at one or more doses of ST in cattle have not been reported. It would seem possible, and has been suggested (Crooker et al., 1990), that amino acid availability may have limited the response to exogenous ST in some studies. Evidence to support this is found in the demonstrated additive effects of abomasal casein infusion and daily bST administration on nitrogen retention in growing steers (Houseknecht et al., 1992) and lambs (Beermann et al., 1991) and in observed additive effects of fishmeal and ovine ST (oST) on feed conversion efficiency and hind leg muscle weights in growing lambs (Beermann et al., 1990).

The Net Carbohydrate and Protein System model developed by Fox and co-workers (Fox et al., 1992; Russell et al., 1992; Sniffen et al., 1992) was used to compare nutrient requirements of control and ST-treated steers in which nitrogen retention was increased 32.6 percent in the absence of abomasal casein infusion and increased an additional 44.6 percent with abomasal casein infusion (Fox et al., 1990a). After input of body weight, frame size, sex, condition, and breed designations, frame size was adjusted for bST-treated cattle to bring the predicted gain to equal observed gain. Predicted microbial protein production and amino acids

provided from feed were then used to predict protein gain and to compare these values with observed nitrogen retention. Predicted and observed values were in good agreement. Analysis with the model indicated that increased energy intake accounted for 5.8 percent of the response, change in composition of gain accounted for 8.1 percent, and increased efficiency of ME use accounted for 9.5 percent of the residual response. Although these are preliminary data from use of a model that has not been extensively validated, these results led to the conclusion that increased efficiency of use of absorbed amino acids for protein gain accounted for the other 75 percent of the increase in protein gain (nitrogen retention). These results would lead to the generalization that a diet balanced to meet amino acid requirements for large-frame (large mature size) cattle, as indicated by the NRC's 1984 requirements, would be adequate for support of the magnitude of response to bST observed in this study.

Few data are available to determine whether mineral requirements in growing cattle are altered with ST treatment. Eisemann et al. (1986a) found serum concentrations of calcium, phosphorus, and magnesium to be normal in bST-treated heifers. House et al. (1989) observed no change in copper, manganese, and zinc absorption in heifers treated with different amounts of bST; but retention of copper tended to increase with bST dose, and sulfur retention was increased about 30 percent at the highest dose.

Effects of bST or oST in Growing Lambs

Average daily gain is increased between 10 and 20 percent with daily administration of BSI (Wolfrom et al., 1985; Pullar et al., 1986; Johnsson et al., 1987; Pell and Bates, 1987; Zainur et al., 1989) or oST (Wagner and Veenhuizen, 1978; Wise et al., 1988; Beermann et al., 1990) in growing lambs. Feed intake was not significantly altered in most studies, and feed conversion efficiency was increased by 14 to 20 percent in at least four of the studies that reported significant increases in gain and composition of gain. Short-term (30 days) treatment of ram lambs with bST did alter composition without improving growth performance in one study (Rosemberg et al., 1989). Observed increases in carcass lean content ranged from 5 to 25 percent, although no change was observed in a few studies. Significant reductions in carcass or empty-body fat have been observed in nearly all studies. Gain, feed conversion efficiency, and composition changes all exhibited linear dose-response relationships in growing lambs administered 0, 50, 100, 150 or 250 µg bST/kg body weight/day (Zainur et al., 1989).

Few data are available to determine whether nutrient requirements are altered with ST treatment in growing lambs. Carcass protein accretion rate was increased 36 percent in cross-bred ewe and wether lambs administered 160 µg oST/kg live weight for 56 days without an increase in daily feed intake (Beermann et al., 1990). Lipid accretion rate was reduced 30.4 percent and ash accretion rate was increased 18 percent. As an indicator of skeletal muscle mass change, semitendinosus muscle weight was increased 18 percent. The relative increase in carcass or empty-body protein accretion rate observed in this study is approximately one-half that observed in growing pigs treated with similar doses of pST (see Chapter 5). One explanation may be that absolute amount or balance of individual amino acids available at the site of absorption may limit the response of growing lambs (and other ruminants) to ST treatment.

An attempt was made in the study by Beermann et al. (1990) to improve amino acid availability through addition of fishmeal to the diet in half the lambs receiving oST, human GRF (hGRF), or excipient. Replacement of an equal amount of soy protein with fishmeal protein (present at 4 percent of the diet) resulted in an additive effect with oST on feed conversion efficiency and proximal hind leg muscle weights (Beermann et al., 1990). ST improved feed: gain 20 percent, in addition to the 20 percent improvement achieved with fishmeal.

Results from recent studies with growing lambs (Beermann et al., 1991; MacRae et al., 1991) are in agreement with the results from similar studies with growing steers (Houseknecht et al., 1992), demonstrating that abomasal casein infusion and exogenous bST increase nitrogen balance in an independent and additive manner. Abomasal casein infusion (4 to 5 g/day) increased nitrogen balance 42 percent, and twice daily administration of 100 µg bST/kg body weight increased nitrogen balance 33 percent in wether lambs (28 kg body weight) fed a mixed concentrate diet at 85 percent of ad libitum intake (Beermann et al., 1991). The combined treatment increased nitrogen balance 89 percent. Administration of bST did not alter dry-matter or nitrogen digestibility; however, the efficiency with which lambs retained consumed nitrogen was increased. The percentage of consumed nitrogen that was retained was increased by bST from 23 to 31 percent when lambs received abomasal water infusions and from 27 to 34 percent when casein was infused into the abomasum. MacRae et al. (1991) observed no increase in nitrogen retention when nutrient infused sheep were administered ST at near nitrogen equilibrium, but a 25 percent increase was observed when nitrogen intake was increased. The percentage of infused nitrogen that was retained also increased with bST administration. These data agree with the apparent increase in efficiency with which consumed protein was deposited in the carcasses of lambs injected with oST (Beermann et al., 1990) and with similar results in growing pigs fed increments of protein in isocaloric diets (see Chapter 5). These data suggest that feeding strategies that provide adequate quantity and balance of amino acids may be needed to maximize the response to ST, despite the apparent improved efficiency with which amino acids are used for protein deposition. At this point, it can be speculated that if amino acid balance in the diet meets requirement profile, only minimum changes in nutrient

requirements for energy and protein would result with ST treatment. If intake is influenced by ST dose, nutrient density of diets may have to be increased to compensate. It remains to be demonstrated whether amino acid availability or balance (or both) limit the protein deposition response to ST in growing lambs and cattle fed conventional complete, mixed concentrate diets. Neither stepwise restriction of energy intake nor protein intake have been reported in lamb ST studies. Significant increases in weights of major organs such as liver, kidneys, and heart (Muir et al., 1983; Zainur et al., 1989; Beermann et al., 1990) indicate that small increases in maintenance requirement may be present. This increase is associated with proportional increases in organ and lean tissue weight, which resulted in more total lean tissue or protein mass per unit body weight. There is no apparent increase in maintenance requirement per unit of lean tissue in growing ruminants administered ST.

Effects of GRF in Growing Cattle and Lambs

Limited data are available that describe long-term effects of GRF administration on growth and composition in growing cattle (Ringuet et al., 1988; Enright, 1989) and lambs (Wise et al., 1988; Byrem et al., 1989; Beermann et al. 1990). Multiple daily subcutaneous administrations of 5 µg hGRF/kg body weight increased average daily gain 13 percent and decreased feed: gain 18 percent in growing wether and ewe lambs treated for 6 or 8 weeks (Beermann et al., 1990). Doubling of the dose reduced feed intake 6 percent and resulted in no improvement in ADG. Carcass protein accretion rate was increased 30 to 35 percent, lipid accretion rate decreased 21 to 28 percent, and ash accretion rate increased 30 percent. Lambs in this study were fed a diet containing 16 percent crude protein and adequate energy. Subcutaneous infusion of a hGRF analog into lambs for 28 days increased rate of gain 16 percent and improved feed conversion 18 percent without effect on feed intake, wool growth, or carcass weights (Godfredson et al., 1990). Treated lambs contained less fat. A similar response was obtained with subcutaneous infusion of hGRF in wether lambs for 5 weeks (Byrem et al., 1989). Because the data indicate that responses nearly equal those achieved with ST administration, similar conclusions must be drawn for effects on nutrient requirements in lambs.

Effects of GRF on energy and nitrogen metabolism were recently investigated in growing beef steers fed a 75 percent concentrate diet at two levels of intake for 3 weeks (Lapierre et al., 1992). GRF treatment increased nitrogen retention 108 and 80 percent at the low (approximately 88 g/day) and high (approximately 159 g/day) levels of nitrogen intake. A significant increase in digestibility was observed, but most of the improvement resulted from reduction in nitrogen excretion and from the significant (approximately 50 percent) increase in efficiency of nitrogen utilization that was observed at both levels of intake. Measurements of energy and nitrogen metabolism in the portal drained viscera and liver in these steers demonstrated reduced amino acid extraction ratio and reduced net uptake of amino acids by the liver (Reynolds et al., 1992). GRF decreased the amount of energy lost in the urine and feces, but this was countered by increased heat production. Total tissue energy retention was not altered, but energy retained was repartitioned toward 67 and 19 percent less body lipid at the low and high intakes, respectively. The authors concluded, based on calculations, that maintenance energy costs and the efficiency of ME use for tissue deposition were not altered by GRF.

Taken together, results from recent studies suggest that protein (amino acid) availability and amino acid profile may be important factors influencing the magnitude of protein deposition response to ST or GRF administration in growing ruminants. The large absolute increases in protein synthesis and deposition rates observed in ST-or GRF-treated animals have occurred when protein nutriture was considered in the design of the experiment. Enhancing amino acid availability enhances the protein deposition response, and the expected increase in dietary protein or amino acid requirement is offset by increased efficiency of nitrogen utilization. Houseknecht and Bauman (1992) used data from five separate studies to calculate the biological value of consumed protein (grams of nitrogen retained per gram of nitrogen absorbed) in cattle or lambs treated with ST or GRF. The biological value was increased by 20 percent to as much as 70 percent in treated animals. This increased biological value appears to result from reduced amino acid oxidation and a major site of reduction appears to be the liver. Carefully designed studies will be required to elaborate the integrated effects of species, stage of growth, genotype and gender, and dose of ST or GRF on nutrient requirements of growing ruminants.

Summary of Effects of Somatotropin and Growth Hormone Releasing Factor in Ruminants

Well-designed experimental approaches to address the question of whether nutrient requirements are altered with exogenous ST administration in cattle, lambs, or other ruminants need to be conducted before meaningful recommendations can be made. Dose-response relationships between growth performance and composition of empty-body gain have not been comprehensively evaluated to determine influences of genotype, gender, and stage of growth. Data from several studies suggest that the smaller protein accretion rate and nitrogen balance responses observed in ruminants administered ST or GRF, compared with responses in swine, are caused by constraints on quantity or balance of amino acids available at the site of absorption. However, ST or GRF administration in ruminants effectively increases the calculated biological value (gram of retained nitrogen

per gram of absorbed nitrogen) of consumed proteins. This appears to be the result of direct effects on the liver to decrease the extraction ratio and net removal of amino acids from the circulation (an amino acid sparing effect). It is not currently possible to define requirements or formulate diets that deliver the appropriate balance and quantity of amino acids to match the increase in protein accretion rate in ruminants, as can be done for nonruminants. Quantity and balance of amino acids exiting the rumen are not easily predicted or determined because of the alterations that occur during rumen fermentation. The magnitude of protein accretion rate and decrease in lipid accretion rate are also influenced by dietary energy levels, gender, age, and breed of cattle and sheep. To allow for nutrient adequacy assessment, future studies must include careful consideration and detailed description of diets and animals used. Ultimately, studies designed to assess protein and energy requirements using empty-body protein (amino acid), lipid, and mineral accretion rates as response variables must be conducted to accurately and adequately define nutrient requirements in growing ruminants. Because the mechanism(s) by which ST alters growth performance and composition of gain appear to be similar in growing ruminants and pigs (Chapter 2), dietary manipulations for use of ST in ruminants should be based on the responses to alterations that have been demonstrated for growing pigs treated with pST (Chapter 5).

EFFECTS OF β-ADRENERGIC AGONISTS

There are relatively few data on which to base sound conclusions or predictions of the nutrient requirements of growing ruminants receiving *β*-adrenergic agonists. Systematic investigations into the protein and energy requirements of growing or finishing cattle or sheep have not been conducted. These important data are also limited for swine (Chapter 5) and poultry (Chapter 6). Defining these requirements requires (1) applying current knowledge regarding mechanism of action, growth performance, and composition of gain results determined over a range of protein intake when energy is not limiting and (2) determining whether altering the balance of available amino acids influences the efficacy of the *β*-adrenergic agonists for their effects on protein deposition rate. A detailed discussion of the biological basis of amino acid and energy requirements in growing animals has recently been published (Reeds and Mersmann, 1991) in which the authors also address the important issues regarding assessment of nutrient requirements in animals fed *β*-adrenergic agonists. Use of a wide range of protein intakes and the break-point analysis, which has been employed to define the nutrient requirements of swine receiving pST (Chapter 5), has likewise been applied to growing swine fed *β*-agonists (Dunshea, 1991). Although appropriate, studies designed to investigate the effects of postruminal protein infusion on protein deposition response in ruminants fed *β*-agonists have not been reported.

Extrapolation from results of ST studies in growing ruminants to the *β*-agonist-treated ruminant is logical and may be appropriate, with one exception: the significant increase in weight of the liver and kidneys caused by ST treatment is not observed with *β*-agonist administration, although increased energy expenditure has been observed [see reviews by Reeds and Mersmann (1991) and Beermann (1993)]. As is the case for administration of ST, composition of gain and tissue requirements of gain must be known across the range of genotypes, stages of growth, gender, and dose when feedlot diets are used for cattle and lambs. These are not currently available. Also, the quantity and balance of amino acids provided by rumen fermentation must be understood and accurately predicted across a wide range of diet formulations currently used in commercial beef and lamb production before diet alterations can be recommended. Although models are being developed, these models must first be validated for the range of commercial situations to which they will be applied.

Another important consideration for defining nutrient requirements in ruminants fed *β*-adrenergic agonists that alter composition is that they do not chronically alter feed intake, as is the case with ST administration to lactating dairy cattle (increase) or finishing steers (decrease). In most studies, feed intake is not altered, although rate and efficiency of gain are improved, albeit in a transient manner in some instances (Beermann et al., 1986a; see reviews by Boyd et al., 1991; Beermann, 1993).

The efficiency with which energy and protein are used for protein accretion declines with increasing age or weight of the growing ruminant (Black and Griffiths, 1975) and is influenced by sex, genotype, and environmental differences. Dietary modifications used to study these effects in growing lambs administered ST or GRF have also been investigated using *β*-adrenergic agonists. Addition of fishmeal to the diet of lambs treated with oST improved feed conversion efficiency in an additive manner with ST when compared with the conventional diet containing soy protein as the predominant protein source (Beermann et al., 1990). Similar effects on feed efficiency were not observed in growing-finishing lambs fed cimaterol (Beermann et al., 1986a). However, fishmeal increased the weight of individual skeletal muscles in the hind leg by 15 to 19 percent over a 10-week growing period and the effects were additive with the 20 percent increase caused by cimaterol. Hind leg muscles from lambs that received both fishmeal and cimaterol were 40 to 45 percent heavier than the same muscles in lambs that received neither. These data suggest that providing adequate quantity and/or quality of absorbed nitrogen may also be important prerequisites to achieving maximum response with *β*-agonists in ruminants.

Experiments must be conducted to establish the relationships between levels of dietary protein and energy intake in growing ruminants fed *β*-adrenergic agonists to empirically determine nutrient requirements. It cannot be assumed that the increased efficiency of protein use for muscle growth that is observed in lambs (Beermann et al., 1991) and steers (Houseknecht et al., 1992) treated with bST will be observed in ruminants fed *β*-agonists. Detailed characterization of diet formulations and factors that influence nutrient requirements must accompany the composition-of-gain data obtained across the potential application dose of the individual *β*-agonist being investigated. Until these studies have been completed, diets for ruminants should be formulated to take into account the energy requirements associated with increasing empty-body or carcass protein accretion to the magnitude expected with administration of the *β*-agonist. Whether additional nonprotein energy should be fed to these animals remains an open question.

Mineral requirements are not expected to be altered because neither bone mass nor length is altered in ruminants administered *β*-agonists (Beermann, 1993). Impact of environmental fluctuations on nutrient requirements of growing ruminants have not been evaluated but may be important (Fox et al., 1988). The Food and Drug Administration has not approved any of the *β*-adrenergic agonists for use in growing or finishing ruminants.

Summary of Effects of β-Adrenergic Agonists in Ruminants

Larger increases in carcass protein deposition and skeletal muscle growth have been observed in growing cattle and lambs fed select *β*-agonists than have been observed with ST or GRF administration, without obvious differences in diets. Furthermore, visceral organ weights are not increased with *β*-agonists, suggesting that conservation of amino acids may occur and an altered pattern of dietary amino acids may be required for optimizing protein deposition with *β*-agonists as compared with ST or GRF. The question of whether *β*-agonists improve efficiency of protein utilization for protein deposition in growing ruminants, as has been demonstrated for ST and GRF, is unresolved. Although efficiency of energy use is unaltered, whether energy intake requirements are altered is also unknown. Systematic evaluation of energy and protein (amino acid) requirements in ruminants fed *β*-agonists must be conducted before meaningful conclusions can be drawn and accurate predictions can be made.

EFFECTS OF ANABOLIC STEROIDS

The same considerations given for determining effects of ST, GRF, or *β*-adrenergic agonists on nutrient requirements in growing ruminants must be extended to administration of anabolic steroid implants. Significant limitations exist in the data from lamb and cattle experiments in which nutritional manipulations were conducted. Either titration of energy or protein requirements involved too few intervals, or accurate determination of composition of gain was not conducted. It appears that anabolic steroids increase feed intake and increase the live weight at which a similar physiological maturity (percent body fat) is reached (Perry et al., 1991). Special diet formulations have not been required to achieve significant improvement in rates of gain or feed efficiency in growing ruminants implanted with anabolic steroids.

Preston and Burroughs (1958) demonstrated that diethylstilbestrol-treated lambs achieved the greatest improvement (32 percent) and absolute average daily gain when fed a high-energy diet containing 17 percent crude protein, compared to 13 and 9 percent crude protein diets. Feed conversion efficiency was also maximized with this diet, compared to other protein and lower energy combinations, but the lack of a plateau among protein levels suggests that nutrient adequacy was not unequivocally demonstrated. Variability in carcass composition also existed among the treatment groups. Although dressing percentage and rib eye area may be consistently increased by trenbolone acetate-estradiol implants (Bartle et al., 1992), carcass measurements of fat thickness, percentage kidney and pelvic fat, and longissimus (rib eye) area are insufficient indices of composition of gain to assess the question of altered nutrient requirements in ruminants treated with anabolic steroids.

Significant improvement in empty-body weight gain was observed in very young (119 kg live weight) British Friesian steers fed a silage diet substituted with increasing concentrations of fishmeal (0, 50, 100, and 150 g/kg diet) (Gill et al., 1987). Estradiol-17β implants increased daily gain, but only when fishmeal was supplemented in the silage diet (13.75 percent crude protein) at 100 or 150 g/kg diet. The interaction was significant and was associated with increased dry-matter intake in implanted steers (gain was 0.77 kg/day with silage alone). Fishmeal increased empty-body and carcass protein, and the effects appeared to be additive with the estradiol implantation. Fat content was not altered with estradiol implants or with fishmeal. These data suggest that improved balance of nutrients may be required to facilitate growth potential and response to anabolic steroids, if nutrients are limiting. Similar relationships were observed in fattening steers and heifers fed a silage diet with or without fishmeal (Lowman and Neilson, 1985).

Estimates of the effects of anabolic steroids on maintenance indicate there is little change. Lobley et al. (1985) observed no increase in heat production in steers administered a combined trenbolone acetate-estradiol implant that dramatically increased live weight gain and nitrogen retention. Lemieux et al. (1988) and Solis et al. (1989) reported that estimates of net energy for maintenance were decreased by only 1 to 3 percent in implanted cattle. They also reported

that estimates of net energy for gain are reduced 14 to 20 percent with anabolic steroids in cattle. These estimates reflect the shift in the proportion of absorbed nutrients used for protein deposition versus lipid accretion as well as partial efficiency differences in gain of lean versus fat.

Summary of Effects of Anabolic Steroids in Ruminants

Significant increases in ADG (up to 23 percent) have been observed in cattle fed conventional high-concentrate diets and implanted with combinations of anabolic steroids. Increase in dry-matter intake appears to account for a large portion of this response. Maintenance requirements are not increased and adequate data are not available to determine whether nutrient requirements of growing ruminants administered anabolic steroids are different from those found in NRC publications. Published results suggest that enhancing amino acid availability and/or pattern of absorbed amino acids will improve protein deposition rates in growing cattle. Achieving maximum protein deposition rates with anabolic steroid implants may necessitate developing strategies to remove the constraint suggested above. Considerable additional research is required to determine the importance of nutrient balance, particularly amino acid availability and balance, in supporting greater protein accretion rates in ruminants treated with anabolic steroids. Assessment is complicated by the lack of control we now have over the profile and amount of amino acids provided by the rumen that are also available for supporting protein accretion. Studies conducted and published in the future must include detailed descriptions of the diets used to allow nutrient adequacy assessment. In addition, studies specifically designed to assess protein and energy requirements of growing ruminants administered anabolic steroids must be conducted using empty-body and/or carcass protein accretion rates as response variables to accurately and adequately achieve these objectives.

5

Effect of Metabolic Modifiers on Nutrient Requirements of Growing Swine

The productive efficiency of swine raised for pork production is determined, to a large extent, by the proportion of nutrients used for fat versus muscle accretion. Nutrient partitioning is influenced by genotype, gender, hormones, and stage of growth as well as by feeding management. Recent advances in biology have made it possible for animal scientists to dramatically alter growth and development patterns by modifying the animal's metabolism. Porcine somatotropin (pST) and β-adrenergic agonists (β-agonists) are metabolic modifiers that have allowed scientists to investigate and modify how farm animals use absorbed nutrients for growth. Unprecedented responses in protein and lipid accretion have been reported (Campbell and Taverner, 1988; Evock et al., 1988; Boyd and Krick, 1989).

The availability of metabolic modifiers presents an important nutritional challenge because each metabolic modifier differs in its mode of action, and these differences can result in considerable variation in the rates of lean tissue deposition. This suggests that a systematic method for determining nutrient requirements must evolve to accommodate a widening range of biological and nutritional situations. Therefore, any experimental or empirical attempts to estimate a particular nutrient requirement should contribute quantitative information and knowledge of biological principles such that mathematical relationships could then be used in dynamic, computer models (factorial approach).

In this chapter somatotropin (ST) and β-agonists are discussed in the context that their use may change intermediary metabolism of treated pigs such that nutritional requirements might be altered. A systematic approach is possible with pST because the data are extensive and accommodate a dynamic, computer simulation approach. Little quantitative information is available about the effects of β-agonists on nutrient requirements, but there are some potentially important differences when β-agonists are compared with somatotropin. Care is taken to illustrate how the experimental approach in estimating nutrient requirements can simultaneously accommodate the objectives of estimation and definition of mathematical relationships. Emphasis will be placed on dietary protein (amino acids) and energy because the available information almost exclusively addresses one or both of these nutritional entities.

NUTRITIONAL IMPLICATIONS OF METABOLIC MODIFIERS

The growth response to metabolic modifiers is best illustrated with pST because both treated and untreated pigs have been well characterized. The effects of pST administration on growing swine have been documented for two phases of growth —growing and finishing—in which intrinsic differences exist for protein and lipid accretion (Boyd et al., 1991; see Table 5-1). Although pST is effective in diverting nutrients away from lipid accretion and stimulating protein accretion during the early growth phase (approximately 20 to 50 kg body weight), the greatest relative response has been observed during the later growth stage or finishing phase (approximately 50 to 100 kg body weight). The biological basis for this is unclear but the potential impact on nutritional requirements is most evident for the finishing phase of growth. First, the effect of pST on depressing lipid accretion (grams per day) is much greater than the increase in protein accretion (grams per day) (see Table 5-1) which, overall, results in a lower caloric gain and, concomitantly, a decline in energy intake. This implies that the nutrient-to-energy ratio must increase to ensure a constant intake of nutrients. Second, an increase in the rate of protein deposition requires increased daily amino acid intake, and an increase in the proportion of total body protein requires an increase in total amino acid intake. The extent to which this is true, however, depends on whether pST alters a pig's ability to digest and absorb amino acids and/or its metabolic efficiency in using absorbed amino acids for

protein accretion (called biological value or partial efficiency). In addition, the mineral content of diets must be considered because dramatic changes have been observed for ash accretion rate (Caperna et al., 1989; Bark, 1990). The potential impact, however, on the requirement for vitamins is not predictable from available data.

TABLE 5-1 Responses of Swine Administered Porcine Somatotropin (pST) during Two Phases of Growth

	Growing Phase (20–50 kg BW)			Finishing Phase (50–100 kg BW)		
Variable	Control	pST	% Change	Control	pST	% Change
Protein accretion, g/day[a]	120	150	25	135	235	74
Lipid accretion, g/day[a]	207	122	-41	340	60	-82
Ash accretion, g/day[a]	21	25	19	16	26	62
Muscle yield, kg	—	—	—	31.4	42.8	36
Fat yield, kg	—	—	—	23.2	6.0	-74
Growth rate, g/day	900	990	10	1,140	1,330	17
Growth efficiency, F:G	2.3	2.0	-13	3.0	2.0	-33
DE intake, Mcal/day	7.3	6.7	-8	13.3	10.2	-23

NOTE: Animals used were females and castrate males (8 to 10 per treatment) fed diets adequate in protein (Krick et al., 1990, 1993). The pST dose used (150 µg pST/kg BW/day) maximized protein deposition. DE, digestible energy; F:G, feed to gain ratio;—, not available.

[a] Whole-body deposition rates determined by comparative slaughter.

Source: Boyd et al. (1991).

The need for a more dynamic approach for estimating amino acid requirements and perhaps other nutrients is suggested by data presented in Table 5-1 and Figure 2-2. This information shows that marked differences in nutrient deposition do occur between the early growth and the finishing phase. Further, the response to pST will vary markedly depending on the dose used (see Figure 2-2). Nutrient requirements are generally derived experimentally by relating a physiological response to increments of nutrient input under specific conditions. However, animals are often inadequately characterized beyond age, weight, gender, and genotype. For example, protein accretion rate is seldom specified even though this clearly determines the requirement for a particular amino acid. The factorial approach is a more dynamic way to estimate the amino acid requirement because factorial estimates are not limited to conditions under which they were derived. Thus, factorial estimates are more amenable to changes that occur in genetic base, gender, and technological advancements such as metabolic modifiers. However, an understanding of biological principles and experimentally derived mathematical relationships is required if factorial estimates are to be trusted. A more systematic biological and mathematical view of requirement estimation must be undertaken so that conditions for which the requirement are relevant are better defined and accommodating of such a dynamic status.

Data in Table 5-1 indicate that the rate of protein accretion is considerably below the inherent, genetic capacity and suggests that endogenous secretion of pST in nontreated pigs is not sufficient to support the rate of protein deposition that can be attained. The potential for protein deposition is best illustrated by the elite responders (top 10 percent), which deposited 250 to 270 g/day of protein when treated with pST. This rate of protein accretion, with castrate and female pigs, exceeds previous estimates for intact males by approximately 30 percent (Campbell, 1987; Campbell et al., 1990a), negating the advantage typically acknowledged for the intact male. Thus, the estimated biological potential for protein accretion in finishing phase pigs is at least 270 g/day. The net effect of this alteration was an unprecedented efficiency of growth (feed: gain approximately 1.8) coincident with an equally impressive rate of gain for intact male pigs of an elite genotype that were highly selected for lean tissue deposition (>1,500 g/day; Campbell et al., 1990a). The potential for efficiency of growth in this example rivals commercial broiler chickens.

NUTRITIONAL CONSTRAINTS TO LEAN GROWTH

Although the capacity for protein accretion is determined by genotype, gender, and stage of growth, it is well known that extrinsic or environmental factors such as inadequate intake of either protein (amino acids) or energy may limit the potential for lean tissue deposition. The interrelationship between protein and energy intake and protein deposition has been studied in several species, but data are most extensive for growing swine (Black et al., 1986; Campbell, 1987; Dunkin, 1987). One must assume that metabolic modifiers likewise operate within this framework, until data on biological mechanisms suggest otherwise. Failure to address these nutritional considerations may limit the biological response to metabolic modifiers.

The interrelationship between protein accretion and protein and energy intake is illustrated in Figure 5-1*A*. In the protein-dependent phase, protein deposition increases in a linear manner with each increment of dietary protein intake. Whether the animal is able to reach its potential for protein deposition depends on protein adequacy and also the availability of sufficient dietary energy. For example, if pigs are fed increasing amounts of protein, in conjunction with a fixed amount of energy (E_1), protein deposition increases to an apparent maximum (M_2). Additional increments of protein will not result in a further increase in protein accretion because of an energy constraint. However, when this energy restriction is removed (E_2), protein deposition increases to a new maximum (M_1) allowable by protein intake. M_1 protein accretion would represent the genetically determined maximum, if energy and protein intake are both adequate. Thus, the protein (amino acid) requirement is a function of the level of the protein deposition allowable by energy consumed. Unfortunately, M_1 and M_2 are seldom experimentally defined even though they are important factors in accounting for differences in the protein (amino acid) requirement at a particular energy intake.

An energy limitation is less likely to occur with pigs weighing more than 50 kg because energy intake generally exceeds the expressed capacity for protein accretion (3.5 to 4.0 times the maintenance energy requirement) with ad libitum feeding. In contrast, energy intake may constrain protein deposition for pigs weighing less than 50 kg and perhaps for genetically elite intact males weighing more than 50 kg. The apparent disparity between pigs in early and late stages of growth may be the result of the fact that an inverse relationship exists between nitrogen deposition per unit metabolic weight and body weight (Carr et al., 1977).

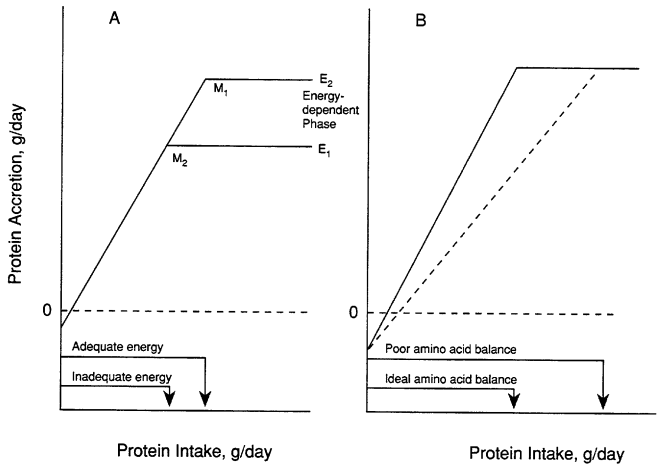

FIGURE 5-1
Interrelationship between protein deposition and protein (amino acid) intake in swine. *A*: Protein deposition under restricted energy intake (E_1) results in an apparent maximal protein deposition (M_2); but when energy intake is not limiting (E_2), a higher maximal protein deposition (M_1) can be achieved. *B*: Effect of protein biological value (BV)—the solid line represents the intake of protein with an "ideal" amino acid pattern for protein deposition; the dashed line represents the response to a protein with an inferior biological value.

The effect of protein quality on the dietary protein requirement for a given level of protein deposition is illustrated in Figure 5-1*B*. The slope of the linear component is determined by the digestibility of dietary protein, the extent to which the amino acid pattern accommodates the tissue requirement (i.e., "ideal" amino acid pattern; Agricultural Research Council, 1981; Taverner, 1987; Wang and Fuller, 1987) and the extent to which absorbed amino acids are partitioned to protein deposition (i.e., biological value). This coefficient is a measure of net protein utility, which in turn determines the quantity of dietary protein required to support a given rate of protein accretion. Any metabolic modifier that enhances protein deposition without altering the efficiency of protein digestion and/or partitioning of amino acids to protein deposition could do so only if there were a concurrent increase in dietary protein intake.

The relationship between energy intake and protein deposition must be precisely defined for both nontreated pigs and pigs treated with metabolic modifiers in order to differentiate between the animal's tissue requirement for protein (M_1, M_2) and the capacity of different dietary regimens to satisfy this tissue requirement (e.g., restricted versus ad libitum feeding). For example, a program of energy restriction attempts to accommodate maximum lean tissue accretion while minimizing fat deposition. This principle is illustrated in Figure 5-2, which relates the pattern of muscle and fat deposition to energy intake for pigs in the 50 to 100 kg body weight range (Whittemore, 1986). Expression of amino acid requirements in relation to a defined optimum for energy intake [e.g., grams of lysine per Mcal of digestible energy (DE) intake] is appropriate when energy is the ultimate determinant of protein accretion. Concomitantly, this ratio accommodates the dynamics of feed intake conceivable

with restricted feeding and the consequent effects on tissue protein deposition. Conversely, with ad libitum energy intake, the tissue requirement for amino acids is independent of energy intake so that the relevant expression of dietary needs is grams per day of a particular amino acid.

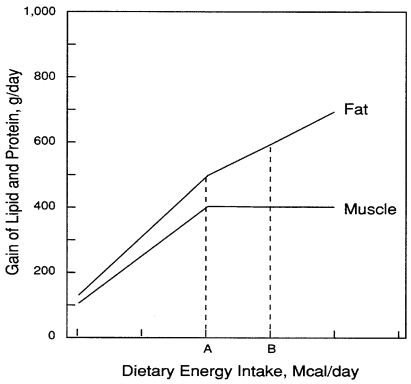

FIGURE 5-2
Hypothetical model originally presented by Whittemore (1986) showing the relationship between dietary energy intake and deposition of muscle and fat tissues. Point *A* represents restricted energy intake to the level just required to maximize protein deposition. Point *B* represents ad libitum feed intake.

EFFECT OF METABOLIC MODIFIERS ON NUTRIENT REQUIREMENTS

Consideration of how nutrient requirements are altered by metabolic modifiers and other new technologies requires a systematic approach to quantitatively define how each of the components of nutrient use is affected. This has been fully described in a recent review by Boyd et al. (1991). The essential components are (1) digestibility, (2) rate and composition of gain (i.e., nutrient deposition), (3) efficiency with which absorbed nutrients are used for tissue deposition, (4) the quantity of nutrients required for maintenance, and (5) level of feed intake. The impact of metabolic modifiers on amino acid requirements and allowable energy intake is discussed within this framework and in the context of ST because these data are most extensive. Particular emphasis is placed on experiments that reveal both biological principles and mathematical relationships.

Any strategy that increases ST concentration in the blood would be expected to affect the pattern of nutrient deposition. Given the current technologies and our understanding of ST biology, there are at least four conceivable approaches to manipulating the ST axis, which have been discussed in recent reviews (Boyd and Wray-Cahen, 1989; Campion and Novakofski, 1990). Also, the argument for a more dynamic approach for estimating nutrient requirements is well illustrated with exogenous administration of pST where the magnitude of response has proved to be a function of dose (see Figure 2-2), gender (Figure 5-3), and genotype (Campbell et al., 1990a; Krick et al., 1992). Thus, information from the pST data base has established the precedent to adopt a more dynamic method for estimating nutrient requirements. This has implications with respect to experimental design considerations and the type of information collected.

Intake

A consistent effect of pST treatment is reduced energy intake (see Figure 2-2 and Table 5-1; see also Table 5-2). Definition of the energy-allowable intake is important under conditions of ad libitum feeding because the nutrient requirement must ultimately be related to expected voluntary intake to ensure that the daily nutrient requirement is met. The extent to which energy consumption is altered, however,

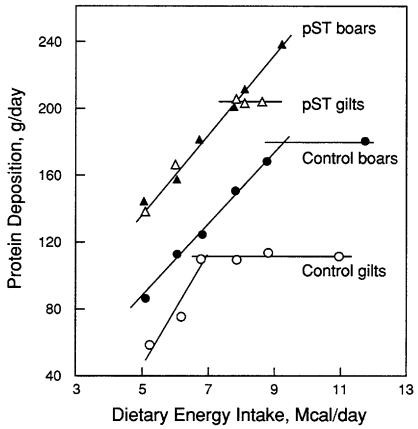

FIGURE 5-3
Differential response of female and intact male pigs to pST treatment and dietary energy intake (Campbell et al., 1991). Pigs (between 60 and 90 kg) were treated daily with pST (90 µg/kg body weight) or excipient. Six levels of energy intake were used that ranged from 5.08 Mcal DE/day to ad libitum. Protein intake was 12 percent above that determined as adequate in a previous study involving intact males of the same genotype (3.7 g lysine/Mcal DE) and level of pST. Carcass protein deposition rates were determined by comparative slaughter.

depends on the energy density of gain allowable by the dose of a particular metabolic modifier. For example, at a dose that maximizes protein accretion, pST reduced caloric gain in growing swine from 3.30 to 1.75 Mcal/day during the 50 to 100 kg phase (see Figure 2-2). Equally striking are the dynamics of pST dose in relation to both intake and protein accretion (Figure 2-2). Thus, voluntary intake must be documented in relation to dose of the particular metabolic modifier when administered under ad libitum feeding conditions; subtle differences exist for pigs on energy-restricted regimens.

TABLE 5-2 Factorial Estimation of the Dietary Protein and Lysine Requirements for Control and Porcine Somatotropin (pST)-Treated Pigs (50-100 kg) Exhibiting Different Protein Accretion Rates

Variable	Control		pST			
Protein deposition, g/day	120	120	145	170	190	215
Change, %	0	0	20	40	60	80
Maintenance protein, g/day	13	13	13	13	13	13
Tissue protein requirement, g/day	133	133	158	183	203	228
Dietary protein digestibility[a]	0.86	0.86	0.86	0.86	0.86	0.86
Biological value[b]	**0.62**	**0.45**	**0.62**	0.62	0.62	0.62
Net protein utilization for growth and maintenance	0.53	0.39	0.53	0.53	0.53	0.53
Dietary "ideal" protein, g/day[c]	248	341	298	345	383	430
Dietary lysine, g/day[d]	16.6	22.8	22.0	25.5	28.3	31.8

NOTE: Data are based on results shown in Figure 5-6.

[a] Dietary protein digestibility is based on estimates provided in *Nutrient Requirements of Swine, Ninth Edition* (National Research Council, 1988c).

[b] Biological value: 0.62 is the efficiency of absorbed protein use for protein deposition and is based on determined values from Figure 5-6 for digestible ideal protein. This value is consistent with Krick et al. (1990) for pST treatment on absorbed lysine utilization. The 0.45 coefficient is closer to the estimates derived by Krick et al. (1990; see Boyd et al., 1991), Wiesemuller (1987), and as computed from Moughan (1991) in untreated pigs fed conventional diets.

[c] This is the minimum level of an "ideal" protein having a perfect amino acid pattern.

[d] Based on lysine composition in protein. Refer to text.

Also, the energy intake versus pST dose relationship may vary with phase of growth and, to a lesser extent, by genotype and gender. For example, pST reduces feed intake of ad libitum fed pigs less (-8 percent) when administered during the early growth phase (20 to 50 kg body weight) than when administered during the finishing phase (-23 percent; Table 5-1). The biological basis for this is not clear but appears to be a reflection of the relative changes in protein and fat accretion induced by pST. The impact on intake may also differ with metabolic modifier. Table 5-3 shows that the β-agonist ractopamine causes intake to decrease only slightly in comparison to pST.

Digestion

The tissue requirement for amino acid deposition is a function of both the need for deposition in tissues and for maintenance. The dietary requirement, however, is a function of the extent to which dietary protein is digested and amino acids absorbed as well as the efficiency with which absorbed amino acids are used for protein deposition. In principle, the effects of ST on energy and protein utilization in farm animals appear to be principally associated with the use of absorbed nutrients (Boyd and Bauman, 1989). It is conceivable, however, that digestion is altered indirectly. For example, a reduction in feed intake could result in a slower rate of passage, which in turn may lead to increased digestibility. This probably accounts for the small improvements in nitrogen and energy digestion observed with pST treatment (Wray-Cahen at al., 1991). The relative advantage observed for digestibility of nitrogen in pigs administered pST compared to control counterparts (87 versus 84 percent for controls), with each group fed ad libitum, was predictable from the reduction in intake (Haydon et al., 1983; see also Verstegen et al., 1990). Thus, little or no difference is expected for pigs already fed via a restricted intake regimen.

Maintenance

pST has been shown to alter the maintenance requirement for both energy and amino acids. The higher maintenance energy requirement for pST-treated pigs (Campbell et al., 1988; Verstegen et al., 1989) appears to be an inevitable consequence of increased protein mass (Dickerson, 1985; Campbell and Taverner, 1988). Therefore, when the maintenance cost is constant per unit of lean tissue, the pST-treated pig will have a greater maintenance requirement because it has a greater proportion of lean tissue at any given body weight. However, an increase of 10 percent of the

increased maintenance energy observed in the pST-treated pig could not be accounted for by increased protein accretion (Verstegen et al., 1989; Noblet and Dubois, 1990; Noblet et al., 1992). This difference appears to be related to changes in metabolic activity of organs. For example, Noblet observed that oxygen consumption of some organs was increased (e.g., 50 percent for liver; J. Noblet, Centre de Recherches de Rennes, INRA, St. Gilles, L'Hermitage, France, personal communication, 1990), which is significant because organ weights have been shown to be increased by 25 to 40 percent (Evock et al., 1988). The relevance of these changes to nutritional requirements of restrictively fed pigs is that an adjustment in intake would be required; however, they are of little practical importance to the formulation of diets fed ad libitum.

Efficiency of Absorbed Nutrient Use

As discussed, the effects of ST on energy and protein utilization appear to be postabsorptive. Consequently, the question of whether dietary protein requirements increase in direct proportion to the level deposited depends on whether a metabolic modifier alters the efficiency with which absorbed nutrients are deposited. Furthermore, this facet appears to be an area of opportunity in that a significant inefficiency appears to exist in amino acid metabolism. For example, the efficiency of absorbed amino acid use for protein deposition is known to be inherently low and variable in conventional diets (e.g., partial efficiency of 0.40 to 0.60; Rerat, 1972; Wiesemuller, 1987; Moughan, 1991). Values on the order of 0.80 to 0.94 have been achieved in growing pigs given semipurified diets and fed to optimum rates of growth (Moughan and Smith, 1984; Wang and Fuller, 1989; Chung and Baker, 1992). Although there is no satisfactory explanation for this inefficiency, involvement of amino acids as substrates for processes other than protein deposition accounts for only a small proportion of this inefficiency. To what extent amino acids may be diverted from oxidation in general is unknown, but the impact on dietary requirements is enormous. There is evidence, however, that ST improves the efficiency of amino acid partitioning to protein by as much as 20 to 40 percent in young growing swine (Campbell et al., 1990b; Boyd et al., 1991), cattle (Houseknecht et al., 1992), and lambs (Beermann et al., 1991). A change of this magnitude would have a pronounced effect on the dietary requirement for amino acids.

Theoretical considerations appropriate for the efficiency of absorbed amino acid use are illustrated in Figure 5-4. If the partial or metabolic efficiency of amino acid use for protein deposition is not altered by a metabolic modifier, then the requirement for a particular amino acid would vary in direct proportion to the protein accretion rate (Figure 5-4*A*). Alternatively, if a metabolic modifier increased the efficiency of amino acid use, then increased protein accretion would be accommodated with proportionally less amino acid input than the conventional animal (Figure 5-4*B*). In fact, an improvement in the partial efficiency of 20 to 40 percent could result in little or no change in the amino acid requirement for metabolically modified animals despite marked changes in the rate of protein accretion.

ESTIMATES OF THE LYSINE AND ENERGY REQUIREMENTS FOR ST-TREATED GROWING SWINE

Amino Acids

Several definitive studies have been conducted to determine the impact of pST on the dietary requirement for protein (amino acids) during the early and later phases of growth (20 to 60 and >60 kg). In general, the effects of pST on protein accretion cannot be fully exploited without an increase in protein (amino acid) intake, but a striking difference

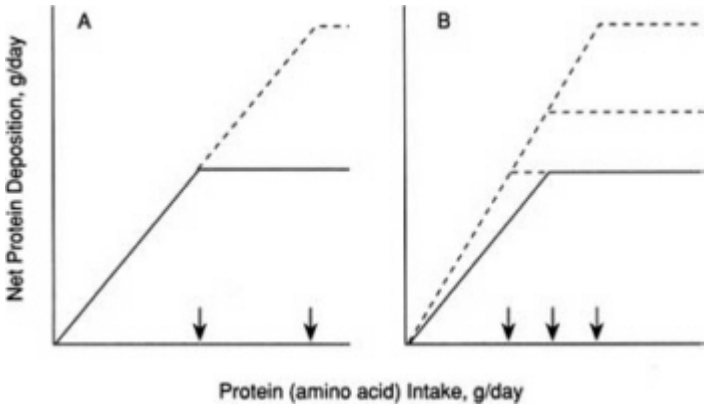

FIGURE 5-4
Theoretical protein (amino acid) dose-response curves for metabolic modifiers. (*A*) A scenario wherein the efficiency of amino acid deposition is not altered; (*B*) a scenario wherein efficiency of amino acid deposition is improved. Scenario *A* would require an increase in protein (amino acid) intake to effect an increase in protein deposition beyond that achieved by a pig not supplemented with a metabolic modifier (solid line). Scenario *B* implies a reduction in protein (amino acid) intake required (dashed line) to achieve a comparable response to a pig not supplemented with a metabolic modifier.

exists in the extent to which the requirement must be increased for the two phases of growth. As previously mentioned, these studies also suggest that pST increases the partial efficiency of amino acid utilization for protein accretion. Particular emphasis will be placed on studies in which protein (or amino acids) dose-response curves were established for both control and pST-treated pigs because such data simultaneously demonstrate the impact of pST on the requirement for protein and the efficiency with which dietary protein is used for protein accretion.

Growing Phase (20 to 60 kg)

Three studies have been conducted to establish the relationship between protein intake and protein accretion in pigs administered pST during the 20 to 60 kg phase of growth. In each study, protein accretion was determined by the comparative slaughter technique in control and pST-treated pigs and regressed on dietary protein intake. These data enable determination of the tissue requirement for and efficiency of amino acid deposition as protein so that improvements in protein deposition can be quantitatively related to required dietary inputs.

Campbell et al. (1990b) used intact male pigs injected daily with either a buffer control or pST (90 µg/kg body weight/day) between 30 and 60 kg body weight. Increments of protein (8 to 23 percent), calculated to provide an ideal pattern of amino acids (Agricultural Research Council, 1981; Taverner, 1987) were added to a diet that was restrictively fed at 88 percent of ad libitum energy intake. The level of dietary protein that accommodated maximum response resulted in a net deposition of 174 g protein/day for pST-treated boars (25 percent higher than controls) as compared with 139 g/day for controls. The most impressive observation was that the rate of protein accretion per unit of dietary protein intake was increased with pST such that the maximal response to pST required only a slight increase in total dietary protein intake (2.4 percent; 17.0 versus 17.4 percent dietary crude protein) to fully exploit the effects of pST on protein accretion and, thus, efficiency of live-weight gain. This equates to approximately 22.0 and 22.6 g lysine/day for control and pST-treated pigs, respectively. In principle, the dietary requirement of lysine may be estimated because amino acids were supplied in an approximately "ideal" pattern. Thus, when protein accretion was regressed on protein intake, pST increased the efficiency of protein use for protein accretion by approximately 25 percent. The absolute estimates for both dietary protein and lysine are anticipated to be slightly overestimated since it has been shown that the Agricultural Research Council's pattern of amino acids is low in sulfur amino acids, threonine, and tryptophan (Wang and Fuller, 1989; Chung and Baker, 1992). This would not affect the conclusion regarding relative differences in the requirement between treatments, however.

Similar observations (Figure 5-5) were also reported by Krick et al. (1993) in a study in which castrate and female pigs were administered either control buffer or pST (150 µg/kg body weight/day) between 20 and 55 kg body weight. Increments of protein (6.4 to 23.5 percent), approximating the "ideal" pattern of amino acids established by Wang and Fuller (1989), were added to a diet and fed ad libitum. Dose-response curves for protein accretion and efficiency of gain suggest a minimum dietary lysine requirement of approximately 24 g/day (148 g/day protein accretion) for the pST group compared to 23 g/day (119 g/day protein accretion) for controls. These data likewise suggest that pST increases the efficiency of amino acid use for protein accretion because a marked increase in protein deposition occurred (+24 percent) with little change in the estimated requirement for dietary lysine (2.6 percent). The apparent increase in the efficiency of amino acid use is further supported by the data of Caperna et al. (1991).

Thus, Figure 5-4*B* is a portrayal of the appropriate scenario for the effects of pST on amino acid use during this growing phase. Based on the data presented by Campbell et al. (1990b) and Krick et al. (1993), the biological value of absorbed amino acids appears to increase by approximately 25 percent with pST treatment. The net effect is that the dietary protein (amino acids) requirement for pigs treated with pST during this phase of growth would be equivalent to that recommended for untreated pigs if pST caused a 20

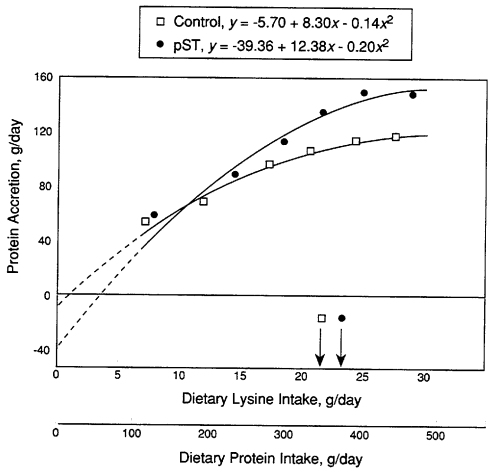

FIGURE 5-5
Dose-response curve for control and pST-treated castrate male and female pigs weighing 20 to 60 kg and receiving increments of dietary protein having an approximately ideal amino acid balance (Krick et al., 1993). The pST selected elicited a maximum response in protein accretion.

percent increase in protein accretion. These results have important practical implications and provide new insight into amino acid use, which warrants further research.

Finishing Phase (60 to 100 kg)

The relationship between protein intake and response to pST during the finishing phase has been examined, but results are less clear than for younger pigs. Clearly the benefits of pST cannot be realized without an increase in dietary protein (amino acids). However, it has not yet been conclusively established whether the protein requirement per unit of protein accretion is unchanged with pST treatment or if the partial efficiency is improved as observed for growing pigs (<60 kg). Three of the studies were designed to quantitatively address this question but results were not in total agreement.

In the study by Campbell et al. (1991), intact male pigs between 60 and 90 kg were injected daily with either a control buffer or pST (90 µg/kg body weight) and were fed diets ranging from 7.3 to 23.8 percent crude protein of an "ideal" amino acid pattern (0.46 to 1.56 percent lysine) (Figure 5-6). Energy intake was restricted (average, 8.53 Mcal DE/day). Whole-body protein deposition increased from 119 to 215 g/day (88 percent) as a result of pST administration. The daily protein intake required to support maximal protein deposition in control and pST-treated pigs was 246 and 357 g/day, respectively. Corresponding lysine intakes were 18.8 g/day (equal to 0.68 percent on an as-fed basis) and 27.1 g/day (equal to 1.20 percent) for control and pST-treated pigs, respectively. For control pigs, the estimate for lysine (18.8 g/day) is slightly lower than anticipated, given the response of the same genotype during the 30 to 60 kg phase of growth, but this may reflect an energy constraint imposed on protein accretion. These data suggest that the plateau for maximum protein accretion was increased with pST treatment but that the biological value was unchanged (0.62). Based on these results, the dietary protein (amino acids) requirement for pST-treated pigs during the finishing phase of growth would increase in direct proportion to the increase in protein accretion rate (Figure 5-6).

Different results were obtained in the study by Krick and co-workers (1990; see also review by Boyd et al., 1991). Protein-response curves were likewise established for both control and pST-treated pigs (150 µg/kg body weight) with a rapidly growing strain of castrate males and females during the finishing phase. Dietary lysine concentrations ranged from 0.35 to 1.56 percent (9.9 to 22.5 percent crude protein) with lysine computed to be first limiting amino acid (Wang and Fuller, 1987; National Research Council, 1988c). Energy intake was not restricted. Whole-body protein deposition increased from 136 g/day for controls to 236 g/day (74 percent) for pST-treated pigs. The daily requirement for lysine was estimated to be 32 and 35 g/day for control and pST groups, respectively (a 17 percent increase). The partial efficiency of lysine use was increased from a low 0.40 in control pigs to 0.60 in pigs receiving pST. This improvement in the partial efficiency of lysine use is in agreement with their previous study with pigs weighing 20 to 55 kg. A similar improvement has also been reported recently in pigs administered pST during this phase of growth (+30 percent; Noblet et al., 1992) and in growing cattle (Houseknecht et al., 1992) and lambs (Beermann et al., 1991). The apparently high estimate for required dietary lysine in control pigs is due to high levels of protein deposition and the relatively low efficiency of absorbed lysine utilization. The latter may have been partially the result of a less than ideal lysine: protein ratio, which varied from 3.5 percent to 5.0 percent over the linear response range (Krick, 1993).

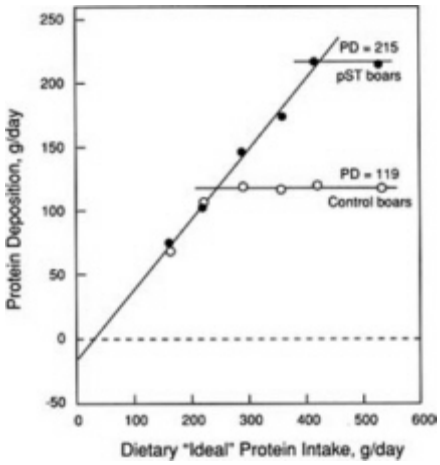

FIGURE 5-6
Dose-response curve for control and pST-treated intact male pigs (treated from 60 to 90 kg) and receiving increments of a dietary protein having an approximately ideal amino acid balance (Campbell et al., 1991). The pST dose used was 90 µg/kg body weight/day. Carcass protein deposition (PD) rate was determined by comparative slaughter.

The studies of Campbell et al. (1991) and Krick et al. (1990) with finishing pigs are in agreement on two critical facets: (1) that the effects of pST cannot be fully appreciated without an increase in lysine and other dietary amino acids and (2) that the efficiency of absorbed lysine use when conventional diets are fed to pST-treated pigs is approximately 0.60. Consequently, the requirements for dietary lysine and ideal protein could be estimated in relation to anticipated improvements in protein deposition. Use of pST at or near the dose optimum for protein deposition (according to the above studies) allows for estimation over a

wide range of potential pST doses. The two studies cited differ, however, with respect to the ability of pST to improve the partial efficiency of lysine utilization by finishing pigs. It is possible that both experiments are correct and that the ability of pST to improve the efficiency of absorbed lysine utilization depends on the partial efficiency achieved through nutritional means. For example, it is possible that pST could not metabolically increase the partial efficiency achieved by Campbell and co-workers (0.62 for absorbed protein use) because it may approximate a "physiological" maximum for the dietary conditions. Alternatively, the low efficiency of lysine use (0.40) observed by Krick and co-workers (1990; see also Boyd et al., 1991) may have allowed for an ST-mediated improvement. This dilemma impacts solely on our ability to predict requirements for nontreated control pigs, since the partial efficiency value is more uncertain than previously believed (0.65; Whittemore, 1986; Boyd et al., 1991). It is not clear whether the relatively higher efficiency of lysine (and protein) use by nontreated pigs in Campbell and co-workers' study as compared to Krick and co-workers and even Wiesemuller (1987; 0.45 to 0.50) is the consequence of differences in amino acid balance or differing endocrine status conferred by the intact male.

Results of less quantitative experiments strengthen the conclusion that the response to pST would be constrained without additional protein intake during the finishing phase (Newcomb et al., 1988; Goodband et al., 1990). Each conducted experiments with female and castrate male pigs in which successive increments of either dietary protein or lysine (diets exceeded anticipated requirement for other amino acids) were added to diets of pST-treated pigs. However, neither group established a dose-response curve for control pigs and assumed the NRC (1988c) minimum recommendation as appropriate for their respective genotypes. Another important difference from the studies discussed previously is that the pST dose used (4 and 3 mg/day, respectively) was below that observed to maximize protein accretion, since the intent was to determine the dietary lysine and/or protein requirement for pigs treated with pST at levels anticipated for commercial use. This is obviously important when making comparisons between different data sets. Goodband and co-workers (1990) suggested that the requirement for dietary lysine to support maximal growth (for a 4 mg/day pST dose) was doubled (1.20 percent dietary lysine or 30 g lysine/day) for pST-treated pigs. This represents a 58 percent increase in the daily requirement but a 35 percent increase for the growth period assumed to be 60 to 90 kg because fewer days were required to reach target weight. Newcomb and co-workers (1988) concluded that the rate and efficiency of gain in pST-treated pigs was maximized at approximately 20 percent protein (or 1.10 percent dietary lysine equivalent).

Comparison between the latter estimates and that of Campbell et al. (1991) and Krick et al. (1990) is not possible because protein accretion data are required to compare estimates at equivalent rates of protein deposition. However, an approximation of the dietary lysine requirement for commercially anticipated levels of pST can be derived from the data presented in Figure 2-2. A dose of 4 mg pST/day would elicit approximately 60 percent of the potential improvement in protein accretion (i.e., 44 versus 74 percent observed at dose maxima; estimated from the pST dose titration curve by Krick et al., 1992). Relating this level of response to the protein accretion portion of Figure 2-2 results in an estimated protein accretion of 196 g/day. This in turn equates to approximately 30 g dietary lysine/day or 1.12 percent dietary lysine based on an actual ad libitum intake of 2.67 kg/day (B. Krick, Department of Animal Science, Cornell University, personal communication, 1990).

Dietary Energy

The question of whether the response to a metabolic modifier depends on a proportional increase in protein input must include consideration of the relationship between energy intake and protein deposition. Knowledge of this relationship is important to determine (1) whether further improvements in protein accretion are constrained by energy intake and (2) whether, and to what extent, energy restriction beyond that induced by the metabolic modifier is appropriate in attempting to match energy intake with lean tissue yield.

Growing Phase (20 to 60 kg)

The relationship between energy intake and protein accretion in growing castrate male pigs administered with pST is summarized in Figures 5-7 and 5-8 (cited from Campbell et al., 1988). Protein deposition increased in a linear manner with each increment of energy intake for both control and pST-treated pigs (Figure 5-7). Porcine ST affected both an increase in line slope and position. Thus, pST is efficacious over a wide range of energy intakes below ad libitum consumption and partitions energy toward protein deposition. Furthermore, there was no evidence of having achieved the plateau for protein deposition for either control or pST-treated pigs, which suggests that energy intake was a common constraint during this phase of growth (25 to 55 kg). The ability of pST to partition energy away from lipid deposition in adipose tissue at each level of energy input may have accounted for the ability to stimulate protein accretion at each level of energy intake (Figure 5-8).

Finishing Phase (60 to 100 kg)

A summary of energy intake-protein deposition response curves for control and pST-treated intact male and female pigs during the finishing phase appear in Figures 5-3 and 5-8. For control groups, protein deposition increased with each

increment of energy intake and achieved a plateau. This is consistent with other studies on pigs during the finishing phase, which demonstrates that protein deposition is not constrained by energy intake regardless of gender or genotype (Whittemore, 1986; Campbell, 1987; Dunkin, 1987).

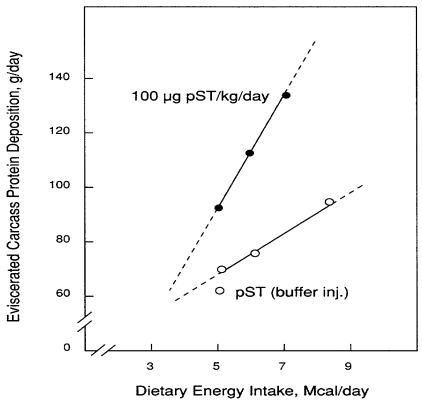

FIGURE 5-7
Carcass protein deposition response of castrate male pigs treated from 25 to 55 kg and treated with pST (100 µg pST/kg body weight/day) or buffer when fed three levels of dietary energy (Campbell et al., 1988). Protein deposition rate was determined in the eviscerated carcass.

With respect to Figure 5-3, maximum protein deposition was greater for male pigs (180 g/day) versus female pigs (112 g/day) and was achieved at approximately 80 percent of ad libitum energy intake (9.56 Mcal/day), whereas maximal protein deposition for gilts was achieved at 62 percent ad libitum energy intake (6.8 Mcal/day; Campbell et al., 1991). Thus, different restrictive feeding regimens would be required to accommodate maximal lean tissue deposition in male, compared to female pigs.

Using information obtained by the comparative slaughter technique, energy retention plots can be constructed to estimate maintenance energy expenditure. The energy retention plots for control and pST-treated female pigs are shown in Figure 5-8. Data are shown for female pigs because the magnitude of the pST response is greater (45 percent increase) than observed for male pigs. Similar calculations for male pigs indicated that pST administration increased maintenance energy expenditure by 30 percent. At energy intakes up to 7 to 9 Mcal DE/day, pST eliminated the effect of gender on protein accretion. This finding is consistent with the results of Campbell et al. (1989a). In the latter study, females were reported to be more responsive to pST with respect to stimulation of growth performance and protein accretion. A biological explanation for this is unclear other than that the intact male elicits near maximal protein accretion and growth in general is more closely synchronized with genetic capacity. Female pigs treated with pST exhibited a plateau for protein deposition at 7 to 9 Mcal DE/day, or 86 percent of ad libitum energy intake, even though protein accretion was 80 percent greater than control females (202 versus 112 g/day). Protein accretion of intact males responded linearly to increased dietary energy intake up to ad libitum (9.56 Mcal DE/day). Consequently, intact males exhibited slightly greater protein accretion capacity (240 versus 210 g/day) beyond that exhibited by females consuming 7 to 9 Mcal DE/day.

It is noteworthy that pigs administered pST and weighing approximately 75 kg exhibit a similar efficiency of growth (1.95 and 1.98 for males and females, respectively) as generally observed for pigs weighing 15 to 20 kg. The regression coefficient for the linear component of the protein deposition-energy intake relationship of pST-treated males and females was also similar to that reported for younger pigs by Campbell and Taverner (1988). Accordingly, the dietary amino acid requirements of pST-treated pigs in the finishing phase might logically be expected to approximate those of pigs weighing 15 to 20 kg. The NRC (1988c) recommends 0.95 percent lysine (2.78 g/Mcal DE) and the Agricultural Research Council (1981) recommends 1.25 percent lysine

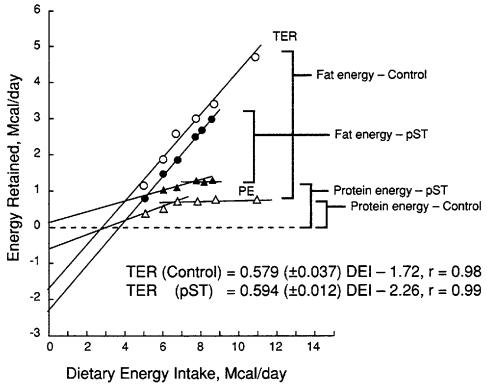

FIGURE 5-8
Effect of digestible energy intake (DEI) on total energy retained (TER) as protein energy (PE) and maintenance energy required (at zero DEI) for control and pST-treated pigs. Dose of pST administered was 100 mg pST/kg body weight/day.

(3.6 g/Mcal DE) for pigs weighing 10 to 20 kg. Levels within this range would appear adequate to support near maximal protein accretion (70 to 75 percent) and growth performance of pST-treated females and castrate males.

Dynamic Estimates of the Lysine Requirement for ST-Treated Swine

Quantitative information as presented in Figures 5-5 and 5-6 may be used to compute the tissue and dietary protein and lysine requirements for various levels of protein accretion. To develop a more dynamic approach we need to know

1. the digestibility of dietary protein (amino acids),
2. how the metabolic modifier alters the rate of protein accretion (plateau of Figures 5-5 and 5-6) and the requirement for maintenance (intercept of Figures 5-5 and 5-6),
3. the pattern of amino acid deposition (e.g., lysine), and
4. the partial efficiency with which absorbed amino acids (protein) are used for deposition and maintenance (slope of line of Figures 5-5 and 5-6).

To derive dynamic estimates for the dietary lysine requirement (DLR, expressed as g/day) the information is interrelated as follows:

DLR= (RLD + OLL) / (BV x DIG),

where, *RLD* is rate of lysine deposition (protein deposition in g/day × percent tissue lysine), *OLL* is obligatory lysine loss (tissue requirement for maintenance lysine), *BV* is biological value or the partial efficiency of dietary lysine use for protein accretion, and *DIG* is digestibility of dietary lysine. The need for a more complete description of experimental conditions with information appropriate for a more dynamic approach is apparent and should be incorporated into the design of future experiments. Ultimately, estimates for nutrient requirements must be related to the expected energy intake to ensure that the requirements for amino acids are met.

A summary of the impact of different protein accretion rates and biological values for amino acid use is portrayed in Table 5-2. This serves as an example of the use of factorial estimation and illustrates how appropriate data from growth studies may be used to address dynamic situations. The impact of metabolic regulation on the dynamics of the "ideal" protein and lysine requirement was calculated using 120 g/day as the baseline rate of protein accretion (Figure 5-6). Whole-body protein accretion rates of 100 and 135 g/day are typical of reported values for castrates and females (Wiesemuller, 1987; Boyd and Bauman, 1989) (Figure 5-5). However, contemporary strains are known to deposit less protein (85 g/day; Wiesemuller, 1987). Proportional increases in protein deposition to 180 and 210 g/day are likely with pST treatment of pigs that have a 120 to 135 g/day base. One must bear in mind that a 40 to 60 percent stimulation of protein deposition may occur with a commercial dose of pST, but the actual level achieved will be a function of dose and base accretion rate for the genotype. These in turn will ultimately determine the dietary lysine requirement. The alternative biological value of 45 percent for untreated control pigs in Table 5-2 reflects the results of Krick et al. (1990; see also Krick, 1993) and Wiesemuller (1987) in contrast to Campbell et al. (1991); hence, the impact on the dietary lysine requirement is the same based on Campbell et al. and Krick et al., but the relative increase predicted in relation to untreated pigs differs.

TABLE 5-3 Expected Field Responses to Porcine Somatotropin (pST) and the β-Agonist Ractopamine

Criteria	Somatotropin[a]	Ractopamine[b]
Growth rate	+12	+9
Feed: gain	-25	-12
Diet intake	-16	-4
Back fat (tenth rib)	-35	-14[b]
Loin area	+28	+15[b]
Dissected tissue mass		
Skeletal muscle	+25	+12[b]
Adipose	-30	-14[b]

NOTE: Values are relative response, percent of control.

[a] Computed from Krick et al. (1992). The pST dose used was 50 µg/kg body weight/day. Tissue mass data were derived from Thiel et al. (1993) using the same pST dose in the same experiment.

[b] Adapted from Veenhuizen and Anderson (1990). Growth performance data are summarized for 12 trials; dissection data represent 24 animals and were expressed as percent of carcass.

The proportion of lysine in pig tissue was 6.7 percent based on analysis of protein for 20 and 60 kg pigs (Krick et al., 1993). This agrees relatively well with previous reports (Campbell et al., 1988; Batterham et al., 1990; Chung and Baker, 1992) but is lower than observed for pST-treated counterparts (7.4 percent; Krick et al., 1993). This apparent increase in lysine content coincided with a reciprocal decrease in glycine. The pattern of amino acids in pST-treated pigs appeared to be otherwise similar. The estimate for maintenance or obligatory protein (or lysine; Figure 5-5) loss was derived at zero lysine (or protein) intake. Dietary lysine is anticipated to remain the first limiting amino acid for ingredients normally used, but preliminary estimates for other selected essential amino acids could not be derived using a validated "ideal" amino acid pattern for untreated pigs (Wang and Fuller, 1989; Chung and Baker, 1992), since the pattern for pST-treated pigs appears to be altered.

The dynamics of gender, genotype, type and dose of metabolic modifier, and feeding strategy make it unrealistic to suggest a single dietary requirement for amino acids for all growing pigs. Consequently, conventional nutrient requirement

tables can only be used as a guide. Only computer-simulated models can integrate requisite animal, environmental, and dietary factors to arrive at biological and economic optimums for dietary nutrients. A number of such models have been developed for growing pigs (Black et al., 1986; Whittemore, 1986; Moughan, 1991).

It is also important to appreciate that nutrient recommendations need to be amenable to "whole-model" production economics. Ultimately, the most appropriate requirement in practice is that which accommodates an economic optimum. It is arrived at by relating predicted responses from nutrient input and associated costs to predicted return. This approach is based on factorial methodology and best accommodates the needs of animal producers.

ESTIMATES OF AMINO ACID AND ENERGY REQUIREMENTS FOR SWINE ADMINISTERED β-ADRENERGIC AGONISTS

β-adrenergic agonists (*β*-agonists) cause reciprocal shifts in protein and lipid accretion, but more quantitative information is needed to determine whether nutritional requirements are changed. Several important differences exist that are examples of factors that must be considered in evaluating the impact of new technologies on nutrient requirements. First, while it is convenient to discuss *β*-agonists in general terms, one must appreciate that each differs structurally. As a result of differences in mode of action, effects on promoting lean deposition and ancillary actions can be expected (see Chapter 2). Second, at least one compound has been shown to elicit a transient response in gain and efficiency of gain. This has not been adequately documented in studies with other *β*-agonists, yet it is a fundamental consideration. Third, *β*-agonists appear to cause a differential growth in that increases in protein accretion are only observed in specific carcass components. This is in contrast to ST, which causes a generalized growth of proteinaceous tissues. This would have a bearing on the pattern of amino acids needed for tissue growth.

Unlike ST, *β*-agonists are orally active and effective at relatively low concentrations (0.5 to 20 mg/kg diet). Their general effect is to increase the rate of skeletal muscle growth, concurrent with a reduction in lipid accretion. Rate and efficiency of growth are generally improved, but differences have been variable and possibly related to differences in effectiveness between compounds, phase of growth, and nutrient provision. Results from 12 studies involving ractopamine hydrochloride fed to castrate male and female pigs have been summarized by Veenhuizen and Anderson (1990) and appear in Table 5-3.

Proper characterization of the response to metabolic modifiers also involves definition of the temporal pattern of growth (i.e., pattern of nutrient deposition). The importance of this is illustrated in Figure 5-9 with the *β*-agonist L-644,969. The data show a declining response in growing swine to this particular *β*-agonist throughout the treatment period (Wallace et al., 1987). A similar response pattern has been observed for growing cattle (Moloney et al., 1990). The difficulty that this poses when either attempting to define required nutrient input or when measuring metabolic or hormone patterns is that the tissue requirement is also in a dynamic flux.

The relative importance of dietary lysine is expected to increase in relation to other indispensable amino acids because intestinal growth is not adversely affected by treatment or by the rerouting of nutrients from adipose to muscle tissue coincident with enhanced muscle growth with *β*-agonist administration (Reeds and Mersmann, 1991). This appears to be a common feature for this class of metabolic modifiers and results in a greater proportion of lysine deposition relative to other amino acids. Thus, lysine would appear to be first limiting and, as such, should be the focus of initial efforts in the evaluation of amino acid requirements. The differential pattern of tissue(s) growth may also confer an advantage in amino acid use relative to ST in that the greater relative allocation of amino acids to muscle confers an efficiency that may affect the amino acid requirement. However, such differential effects on visceral and carcass components may imply a specificity for *β*-agonist effects during the finishing phase of growth when the relative rate of visceral tissue accretion is diminished. This may partially account for the positive response of growth in pigs fed marginal protein diets (12 percent protein; Mitchell et al., 1991).

Although the efficacy and relative responsiveness to the *β*-agonist ractopamine has been established for growing swine (Table 5-3), quantitative information is generally lacking

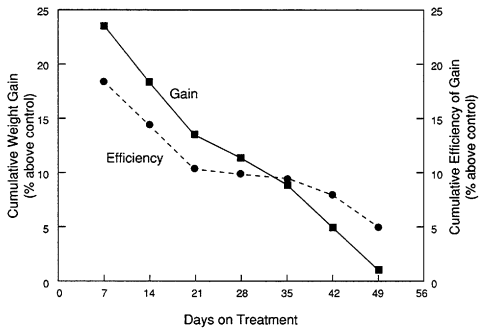

FIGURE 5-9
Temporal pattern of the growth response of pigs administered the b-adrenergic agonist L-644,969 for 7 weeks (Wallace et al., 1987).

for the various components required for factorial analysis, and, concomitantly, little information is available on how nutritional requirements will be altered. Several reports indicate that increases in dietary protein intake are required for the effects of ractopamine to be fully exhibited with respect to composition of gain and growth performance (Anderson et al., 1987; Adeola et al., 1990; Bracher-Jakob and Blum, 1990; Dunshea et al., 1991; Mitchell et al., 1991). To our knowledge, only two studies provide quantitative information on rates of protein deposition in relation to lipid deposition and protein and energy intake (Dunshea et al., 1991; Mitchell et al., 1991).

Mitchell et al. (1991) reported that the ractopamine effect was influenced by dietary protein level and constrained by dietary energy intake if administered during the finishing phase (>60 kg) of growth. However, maintenance energy expenditure was not influenced by the β-agonist. Energy restriction, in a manner and level analogous to previous studies with pST (Figure 5-3), precluded a response in body protein deposition to increments of dietary protein (Figure 5-10). This suggests an apparent inability of ractopamine to depress lipid deposition rate significantly, thereby resulting in an energy constraint of the protein deposition response. This is in contrast to observations with pST.

Dunshea et al. (1991) conducted a systematic protein titration study to determine whether the ractopamine response was caused by increased intake of dietary protein and/or increased biological value of dietary protein. The effects of this and other β-agonists appear to be associated predominantly with the use of absorbed nutrients (Reeds and Mersmann, 1991). Forty-eight female pigs were allotted to one of six levels of dietary protein (8.3 to 23.0 percent) and two levels of ractopamine-HCl (0 and 20 mg/kg). They were restrictively fed to just below the energy requirement for maximum protein deposition (7.1 Mcal DE/day) from 60 kg until slaughter at 90 kg. Estimates for dietary protein requirements were approximately 14.0 and 16.8 percent respectively, to support carcass protein accretion rates of 91 and 112 g/day for 0 and 20 mg/kg ractopamine, respectively (Figure 5-11). Carcass protein deposition rates were not increased by ractopamine at or below 14 percent protein, and the regression slope of protein intake on protein deposition was similar for both treatments. Therefore, the efficiency of protein utilization was not altered as observed in studies with pST with an increase in protein deposition requiring a proportional increase in dietary protein (amino acids). This scenario was previously illustrated for pST (Table 5-2).

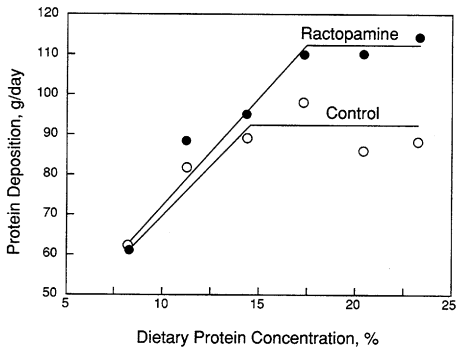

FIGURE 5-10
Protein deposition response of castrate pigs (treated from 60 to 90 kg) to diets containing 12 or 18 percent crude protein fed ad libitum or an 18 percent crude protein diet fed restrictively. Diets contained 0, 20 (12 and 18 percent ad libitum), or 30 (18 percent restricted) mg ractopamine/kg of feed (Mitchell et al., 1991).

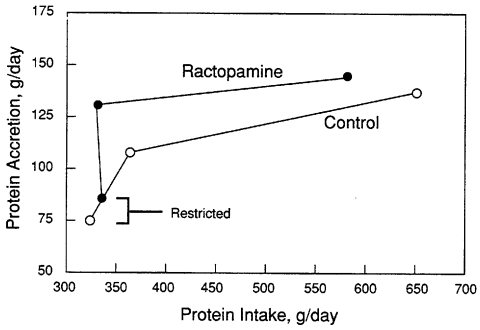

FIGURE 5-11
Relationship between empty-body protein deposition and dietary protein intake in restrictively fed female pigs (7.1 Mcal DE/day) given diets with 0 and 20 mg ractopamine/kg of feed between 60 to 90 kg liveweight (Dunshea et al., 1991).

EFFECT OF METABOLIC MODIFIERS ON MINERAL AND VITAMIN REQUIREMENTS

The increase in the rate of bone ash deposition induced by exogenous pST (Table 2-2; Caperna et al., 1989; Bark, 1990), but not by the β-agonist ractopamine (Bark, 1990), and the structural abnormalities noted in ST-transgenic swine (Pursel et al., 1989) suggest the need for an increase in the daily intake of dietary calcium, phosphorus, and possibly other mineral elements by pigs treated with pST. The rate of bone deposition for pST-treated pigs appears to be a function of dose, with an approximate increase of 35 to 40 percent occurring with 3 to 4 mg pST/day (Bark, 1990). Calcium, zinc, and copper concentration of bone (mg/g dry bone or mg/g ash), however, are not influenced. Therefore,

deposition of specific bone structural elements appears approximately proportional to the increase in growth rate and the corresponding increase in bone mass associated with muscle mass. Assuming that the proportion of dietary minerals absorbed is not altered, a reasonable approach to satisfy this need would be to increase dietary calcium and available phosphorus at a constant rate in direct relation to the expected increase of protein accretion (i.e., 30 to 50 percent).

Because of the similarity in the pattern of nutrient deposition of metabolically modified pigs in the finishing phase and conventional nursery pigs (10 to 20 kg), dietary mineral and vitamin levels based on the estimated requirements of these younger animals may also be appropriate. The possibility for improved digestion, efficiency of use, and the extent to which increased deposition is actually required, versus promoted, are important questions to address. Clearly, this area needs additional research to systematically evaluate the effect of metabolic modifiers.

There is virtually no information relative to the impact of pST or ractopamine on vitamin requirements with the exception of one paper on vitamin D. Typical swine diet formulations contain added vitamin D and fortification levels for other vitamins that are 50 to 100 percent in excess of the minimum NRC (1988c) recommendations. Vitamin D metabolite concentrations differed in serum of pigs treated with exogenous pST (Goff et al., 1990). For pigs consuming a diet fortified with 880 IU vitamin D/kg, sufficient substrate was available to satisfy requirements, and differences observed in vitamin D metabolites reflect either rate-limiting enzymes in the vitamin D-1,25-dihydroxy-vitamin D pathway or represent a concerted adaptation proportionate to long-bone growth. The apparent absence of any other specific vitamin deficiency syndrome in research studies to date indicates there may be no need to further fortify diets with other vitamins beyond correcting for reduced intake.

SUMMARY

Recently developed technologies for modifying protein and energy metabolism provide animal scientists with an unparalleled opportunity to investigate the biochemical and metabolic controls of growth and development. At a practical level, these technologies have the potential to markedly improve the efficiency and competitive position for market share by swine producers. The dramatic effects of pST on protein accretion and thus efficiency of gain depend on markedly different nutrient-to-energy relationships than those that exist for untreated pigs fed ad libitum or restricted intake. A striking difference exists in the extent to which the requirement for amino acids must increase for different phases of growth. An increase in protein accretion of approximately 25 percent during the growing phase is achievable with only a small increase in the requirement for amino acids because of an improvement in the partial efficiency with which absorbed amino acids are used for protein deposition. At present, the effect of pST on protein (amino acid) requirements of finishing pigs is less clear. The marked increase in protein accretion (> 60 percent) cannot occur without at least a 20 percent increase in amino acid intake over nontreated controls. However, it remains to be determined whether the increased dietary requirement is directly proportional to the improvement in protein deposition induced by pST. Elucidation of this issue is important to the successful implementation of exogenous pST administration as a practical and economic means of enhancing the efficiency of meat production in pigs.

This review emphasizes the need for systematic research and gives precedence to studies designed to address the causes of low and variable efficiency of amino acid use. This is the single most important factor affecting estimates of the growing pig's requirements for dietary protein (amino acids) and the ability of a diet to meet tissue demands of pigs either treated or not with metabolic modifiers.

6

Effect of Metabolic Modifiers on Nutrient Requirements of Poultry

As discussed for other species, the basic strategies for influencing growth and development of avian species by modifying metabolism to decrease body fat deposition and increase protein accretion include (1) exogenous administration of species-specific somatotropin (ST), in this case chicken ST (cST); (2) exogenous administration of releasing factors controlling endogenous ST secretion; (3) treating the target species with β-agonists administered orally; and (4) various immunological strategies. In addition, avian species demonstrate the phenomenon of true compensatory growth, which in itself influences growth and development patterns.

STRATEGIES

With limited literature available for citation regarding application of these strategies in avian species, explicit nutrient requirement recommendations are, at best, tenuous. Rather, the approach selected was to briefly review the strategies from a practical perspective as they influence avian growth, citing selected literature, and to suggest a standardized diet that would be appropriate for a range of treatment strategies intended to modify metabolism and body composition. Stated alternatively, the standardized formulation would assure that nutrient intake does not limit biological responsiveness.

Exogenous ST Administration

Practicality aside, academic interest in the use of pituitary and recombinantly derived cST (see Figure 2-1) has been justified as a potential growth promotant and partitioning tool to overcome the increasing obesity problem in broilers. For example, the proportion of broiler production costs expended in deposition of the abdominal fat pad, a by-product of no consumer value, accounts for fiscal cost of $94 million annually for the 20 leading poultry integrators in the United States.

Exogenous administration of ST from mammalian sources is ineffective as a growth promotant in aves (Libby et al., 1955; Glick, 1960; Sell and Balloun, 1960) with the possible exception of a tryptic digest of bovine ST (bST) (Myers and Petterson, 1974). Questionable purity of such preparations, in addition to a hierarchy of ST actions across species, confound interpretation. Buonomo and Baile (1988) have found that high doses of recombinantly derived bST increase circulating levels of insulin-like growth factor-I (IGF-I) and give a transient increase in growth rate and feed consumption with no change in feed efficiency. They found that attenuation of these responses was associated with high levels of circulating antibodies against the heterologous hormone.

Using pituitary cST characterized chemically and biologically, Leung (1986) reported the response of pituitary-intact broilers. At doses of 5, 10, or 50 µg cST/day given intravenously over a 14-day period in 28-day-old birds, a transitory stimulation (20.6 percent diminishing to 6.5 percent) of growth rate was observed as compared to saline-injected controls. Feed efficiency and body composition were reported to be unaffected by cST treatment. Subsequently, Burke et al. (1987) reported that recombinantly derived cST at a dose of 500 µg/kg body weight injected subcutaneously 3 times/day (1,500 µg/day, total) failed to stimulate rate and efficiency of gain in either male or female broiler chicks treated from 2 to 24 days of age. Despite the elevation following injection, of circulating cST by six- to sevenfold in treated birds versus controls, no effect on nitrogen retention or carcass protein and ash content were observed. Speculation was offered (Burke et al., 1987) that as a result of intensive selection for growth velocity in this species, circulating concentrations of cST do not limit growth in aves; therefore, exogenous cST administration is biologically neutral.

More recently, Vasilatos-Younken et al. (1988) reported that intravenous administration of cST episodically at a dose of 123 to 150 µg cST/kg body weight/day administered over

a 10-minute period every 90 minutes at stage of development coinciding with the nadir of basal and episodic endogenous cST secretion (8 weeks of age as reported by Vasilatos-Younkin and Zarkower, 1987) improved rate ($P < 0.07$) and efficiency ($P < 0.01$) of gain over a 21-day treatment regime of broiler-strain pullets. Modest reductions ($P < 0.05$ to 0.09) of indices of body lipid content were observed as compared to saline-treated controls. These changes in carcass fat content were not paralleled by a significant increase of carcass protein content. In contrast, continuous, nonepisodic infusion of cST impaired feed efficiency and had no influence on body fat indices. In several studies by other investigators, the continuous administration of cST resulted in an increase in carcass fat, with no change in growth rate (Cogburn et al., 1989b; Scanes et al., 1990). The significance of these studies is that age of birds and pattern of hormone administration are important considerations for obtaining positive responses to cST administration. In addition, if a pulsatile pattern of daily administration is required to obtain a positive response in birds, this introduces an additional complexity for the development of a delivery system for aves.

Qualitatively, avian species may appear less sensitive to, or a less likely target species for, exogenous ST treatment. However, the retardation of growth velocity and a shift toward excessive fat deposition is observed in broilers following hypophysectomy (King, 1969). Neutralization of circulating cST by passive immunization with cST antisera depressed growth velocity (Scanes et al., 1977). These studies indicate that cST is a factor influencing the physiology of nutrient partitioning; however, pharmacologic treatment of aves is at best equivocal.

Because cST exerts many of its growth and nutrient partitioning effects via IGF-I (Chapter 2), infusions or injections of this mediator have also been examined. Daily injections of 100 or 200 µg/kg body weight recombinant-derived human IGF-I, from 11 to 24 days of age, did not change the rate of gain, feed efficiency, body fat, or protein gain of broiler chicks (McGuiness and Cogburn, 1991). Likewise, the infusion of 100 µg/kg body weight/day of recombinant-derived human IGF-I did not affect rate of gain of a slow-growing brown layer strain; however, IGF-I infusion decreased abdominal body fat (Tixier-Boichard et al., 1992).

Hypothalamic Peptide Releasing Factors

Another strategy also affecting ST-mediated physiology involves the exogenous treatment of aves with hypothalamic peptides that stimulate endogenous ST secretion. These include thyrotropin-releasing hormone (TRH, a tripeptide) and ST-releasing factor (GRF, a 44-amino acid peptide). Both TRH (Harvey et al., 1978; Scanes and Harvey, 1981) and GRF (Leung and Taylor, 1983) have been shown to stimulate cST secretion both in vitro and in vivo.

Leung et al. (1984b) found that a daily intravenous injection of TRH at doses of 1 and 10 µg/day significantly improved rate of gain in 4-week-old broiler chicks. Over the 17-day treatment regimen, rate of gain was significantly increased by an average of 12 percent compared to saline-treated control birds. Serial blood sampling for circulating cST analysis indicated that the cST secretory response to TRH diminished with treatment duration. Based on these effects, the anabolic actions of TRH were attributed to the stimulation of ST secretion and the subsequent effect on metabolism. TRH effects on triiodothyronine (T_3) and thyroxin (T_4) production were discounted because thyroid hormone treatment, per se, depresses performance and cST secretion (Leung et al., 1984a). Ingestion of TRH at a level of 10 mg/kg diet from weeks 3 to 7 of production increased daily gain by 14 percent with improved feed conversion (Cogburn et al., 1989a); however, plasma cST concentrations decreased by 33 percent.

Bolus administration of human GRF at doses of 80 and 320 µg/kg body weight/day increased the rate of body weight gain slightly in 1-to 3-week-old broiler chicks (Baile et al., 1986). Circulating cST and IGF-I were increased significantly over control values; however, neither cST nor IGF-I revealed dose responsiveness. Continuous infusion of GRF had no effect on growth rate and induced pituitary desensitization. Leung (1986) reported that doses of 0.1 and 1 µg human GRF administered intravenously once a day transitorily increased rate of gain in 4-week-old broiler chicks. Over the 14-day treatment regimen, the initial 35 percent stimulation in growth rate observed on day 3 diminished to a 9 percent advantage as compared to control chicks. Such studies are consistent with the known physiological role of GRF, but they also indicate that refractoriness to the treatment could be anticipated with pharmacologic doses.

Phenethanolamine Derivatives

Various analogs of epinephrine have typical cardiac activity, but several have reported striated muscle activity selectively increasing the deposition rate of lean tissue (Chapter 2). Dalrymple et al. (1984) reported that clenbuterol added to the diet of broilers between 4 and 7 weeks of age improved rate (5.1 percent) and efficiency (5 percent) of body weight gain, increased dressed carcass weight (1.1 percent), and reduced body fat content (11 to 15 percent) when used at levels of 1 mg/kg diet compared to control broilers. Abdominal fat pad weight was selectively reduced (8.5 percent) in female broilers, while no effect was apparent in males. Comparative slaughter analysis revealed that nutrient partitioning was altered and the improved performance was the result of increased carcass protein (3.6 percent) and water (2.5 percent) content combined with reduced fat content primarily in females. Minimum effective dose determined from dose-response titration suggested

1 mg clenbuterol/kg diet was necessary to evoke the nutrient partitioning effects.

Merkley and Cartwright (1989) using cimaterol at 0.25 mg/kg diet examined the effects on rate of carcass protein, water, and fat accumulation in female broilers. Cimaterol increased carcass protein and decreased carcass lipid compared to control broilers. Despite these effects on nutrient partitioning, no effects on growth performance were noted. The significant reduction in the size of the abdominal fat pad was concluded to result from a reduction of adipocyte hypertrophy and not hyperplasia. Morgan et al. (1989) fed 1 mg dietary cimaterol/kg diet to broiler chicks from 21 to 56 days of age and also observed no impact on growth rate; however, carcass fat was decreased by 20 percent. Shear force values for cooked breast meat were increased by 27 percent over unsupplemented controls, indicating increased meat toughness.

Another β-adrenergic agonist, L-644,969, has both growth-promoting and nutrient-partitioning effects in broilers (Rickes et al., 1987). A 1 to 3 percent improvement in rate of growth and a 1.5 percent improvement in feed conversion efficiency was concluded to result from a 5 to 6 percent increase in carcass protein concentration. No effect on fat deposition was apparent.

The β-adrenergic agonist, ractopamine, increases rate of gain and efficiency of gain in a dose-responsive manner during the finishing period in turkeys (Wellenreiter and Tonkinson, 1990a). Compared to controls, 44 mg ractopamine/kg diet resulted in a 17 percent increase in rate of gain and an 11 percent increase in feed conversion efficiency. Ractopamine was more effective in hens than toms. The expression of ractopamine effects was improved by increasing the dietary protein above that suggested by the NRC (1984). Ractopamine increased carcass weight, dressing percentage, and leg and thigh as percent of the carcass and decreased the abdominal fat pad as percent of the lean weight (Wellenreiter and Tonkinson, 1990b). In this study, shear values for the pectoralis major muscle were not affected by ractopamine.

Immunomodulation

Theoretically, passive or active immunization of animals against somatostatin would remove the intrinsic negative control over cST secretion as well as thyroid stimulating hormone (TSH) and insulin (Vale et al., 1974). As cST, TSH, and insulin concentrations are all major positive hormonal stimuli for IGF-I and growth, immunological approaches have focused on somatostatin.

Lam et al. (1986) reported that both 4- and 8-week-old broilers treated with sheep anti-somatostatin serum had a marked increase in circulating T_3 and T_4 concentrations compared to chicks receiving normal sheep serum. The effect occurred within 10 minutes of treatment and was sustained about 5 hours. Similarly, passive immunization against somatostatin evoked a marked increase of circulating cST (ninefold more than baseline) within 10 minutes of treatment and remained elevated approximately 90 minutes (Harvey et al., 1986). The effects of prolonged treatment and the consequences on growth and nutrient partitioning have not been reported.

Compensatory Growth

Restriction of feed intake to maintenance energy 6 to 12 days posthatch followed by release to ad libitum intake results in true compensatory growth (fractional growth rate accelerated compared to ad libitum fed controls; Plavnik et al., 1986). During the 8-week production period, restricted chicks weighed slightly more than control broilers resulting in a significant improvement in daily gain. Feed efficiency was improved by 10 percent over the production period in both male and female birds. Total carcass fat was reduced by 17 percent, and the abdominal fat pad size was reduced 30 percent. McMurtry et al. (1988) reported that feed restriction early in life delays the peak of circulating cST from day 12 posthatch noted in control chicks until day 42, coincident with the maximum compensatory growth period of restricted birds. Both circulating T_3 and T_4 concentrations were reduced in restricted chicks. Manipulation of feed intake pattern in broilers was suggested (McMurtry et al., 1988) to result from a delay of physiological maturity, such that intrinsic nutrient-partitioning priority of birds during the finishing phase of growth, typified by fat accretion, is delayed, thereby prolonging the period of maximum protein accretion.

In Ovo Manipulations

An attractive strategy for manipulating broiler growth is the injection of hormones or pharmacologically active substances into the egg to elicit changes in embryonic development that will result in desirable changes in growth characteristics of the chick. Several rationales are being pursued, although little has been published. First, injected substances may speed the growth of the developing embryo so that the hatched chick is bigger. Because there is considerable unused yolk and albumen in newly hatched chicks, a large pool of additional nutrients is available for growth of the embryo prior to hatching. Following hatching, it is presumed that a chick starting at a greater initial weight and growing at a normal fractional rate will have a faster absolute rate of growth (g/day). The second rationale is to deliver an agent to the embryo at a critical stage of development so that the course of development is changed. Two approaches are suggested: (1) increase the number of cycles of division of embryonic myoblasts before fusion so that additional myofibers will be available for hypertrophy in the growing chick; (2) decrease the number of progenitor cells for adipose cells

so that fewer preadipocytes are available for hypertrophy and hyperplasia in the growing chick.

Egg injection systems are becoming commercially available and will facilitate the delivery of pharmacological agents to the embryo. This approach is particularly attractive because manipulation of the embryo is considerably more feasible than injections or implants in the growing chick and could possibly require only one or several injections. Hargis et al. (1989) have administered a single injection of ST into the albumen of 11-day- old eggs and observed an 11 percent increase in body weight of 7-week-old male chicks. The increased growth rate was accompanied by improved feed conversion. Although carcass composition was not altered, in ovo ST administration resulted in fewer adipocytes per gram of adipose tissue, but individual cells had greater volume.

NUTRIENT INTAKE RECOMMENDATIONS

A stated requirement for a given nutrient represents a single point along a dose-response curve that when applied to a well-characterized animal population can, with some reliability, achieve predictable growth performance or targeted composition of body weight gain. Application of metabolic modifiers to a target species, such as broilers, represents a unique challenge to nutritionists because such technologies are not well characterized with respect to the population in general. More important, heterogeneity of the response, whether it be a growth enhancement with no effect on composition or a true change in the priority of nutrient partitioning, confounds nutrient characterization. Therefore, only deductive reasoning applied primarily to protein (amino acid) and energy nutriture can be offered with the rationale that this suggested standardized formulation would not limit biological responsiveness for those strategies that affect nutrient partitioning.

Traditionally, nutrient requirements for broilers have been determined empirically using data from feeding trials. The lowest level of a nutrient that results in optimal growth, feed efficiency, and carcass composition is considered to be the requirement. Because of the short growing period (7 weeks) and relative ease of procuring and conducting research with the growing broiler, accurate requirement data have been developed for many of the nutrients. Historically, dietary recommendations made by the NRC have been divided into three growth periods; starter (0 to 3 weeks), grower (3 to 6 weeks), and finisher (6 to 8 weeks). Because the bird's nutrient requirements do not abruptly change at each of these periods, most commercial broiler producers adjust the nutrient levels more frequently, often 5 or 6 times during the 7-week growth period of a broiler, to keep the diet "least-cost." Multiple diets are necessary for least-cost formulations because dietary protein is expensive and the amino acid requirement (as percentage of the diet or percentage of the calories) decreases with age. From a research perspective, the three dietary divisions suggested by the NRC (1984) are adequate to provide a diet reasonably close to those actually used commercially, yet meeting or exceeding all of the bird's nutrient requirements.

Assuming that the objective of experiments concerning metabolic modifiers is to accelerate the rate of lean tissue growth, amino acid requirements will generally be increased compared to current NRC requirements. Over-formulation of dietary amino acids to ensure adequate supply to support a greater rate of protein accretion may be prudent in some situations because excess amino acids will be deaminated and used for energy. However, it is likely that the action of a metabolic modifier may interact with dietary protein level and that effects seen with unrealistically high levels of protein may be considerably different than those observed with "least-cost" diet formulations supplying only enough protein to meet the amino acid requirement. The influence of high dietary protein to energy ratios on circulating hormone levels and carcass composition is well documented (Rosebrough and Steele, 1985). Thus, our goal should be to use experimental diets with additional nutrient fortification to meet the anticipated increased growth rates and increased percent lean in the carcass without supplying surfeit levels of amino acids.

Modeling Approaches

Ideally, mechanistic models should be used to predict changes in nutrient requirements that occur when metabolic modifiers are used. Mechanistic models are based on known metabolic pathways and a quantitative description of their regulation. Thus, mechanistic models derive nutrient requirements from an accounting of their metabolic sources. Metabolic modifiers would drive changes in intermediary metabolism and thus the model would predict new nutrient requirements. Unfortunately, no mechanistic models have been written for poultry.

Most current models for predicting nutrient requirements of animals with variable rates of productivity are based on a trial-and-error approach using input-output relationships (deductive or factorial approach). The input required to support a given rate of growth at any carcass composition can be estimated if maintenance needs and the partial efficiency of nutrient use for productive processes are known. These conceptual relationships form the basis for several models of nutrient requirements of ruminants. This type of prediction has been largely neglected in growing poultry because it is easy to obtain accurate nutritional requirements by conducting growth trials. Thus, there is a lack of sound experimental data on the amino acid and energy requirements needed for maintenance, lean tissue accretion, and adipose tissue accretion. Using general assumptions for maintenance requirements relative to body size, Scott et al.

(1982) used output-based models to predict energy and protein requirements for growing broilers or White Leghorn pullets. Hurwitz and co-workers (1978, 1980) developed similar models to predict amino acid requirements of broilers. The broiler model predicts amino acid requirements (mg/kcal) considerably lower than those suggested by the NRC (1984) based on growth trials, particularly for tryptophan, lysine, and methionine. Because diets formulated to levels predicted by the model resulted in a large increase in abdominal fat, it can be concluded that the model underestimated the true requirement for at least some of the amino acids. A modeling approach is also limited by lack of accurate information on the changes with age of the amino acid composition of the carcass and the maintenance need for energy and amino acids. Until more accurate information on these parameters across various ages of the growing broiler chick are experimentally determined, input-output based models have limited use for accurate prediction of amino acid requirements of broilers. Input-output models have been useful for demonstrating relative changes in requirements as growth rate and carcass composition change. They predict that, at a given rate of growth, improved composition of gain increases amino acid requirements but have little effect on energy requirements. Thus, amino acid requirements expressed as milligrams per kilocalorie increase with improved composition of gain. Input-output models also predict that increasing the rate of growth by 10 percent increases amino acid requirements 10-fold more than decreasing the carcass fat by 10 percent at a slaughter weight of 2.5 kg.

Another way to model changes in nutrient requirements caused by metabolic modifiers is to use empirically obtained nutrient requirements over a range of growth rates to predict requirements at new rates. Because of the ease of conducting experiments with broilers, the requirements for energy, lysine, and methionine are known with reasonable accuracy during the commercially important first 8 weeks of growth. Although prediction based on empirical relationships is not easily amenable to predicting requirements at a variety of carcass compositions, this procedure has a considerably better data base and requires fewer assumptions than the input-output modeling method.

Empirical Predictions

As broiler chicks get older, their amino acid requirements decrease relative to energy. This is partly the result of a decreased fractional growth rate and partly the result of an increased rate of fat relative to protein accretion. Regression of fractional growth rates calculated from data on male broilers (National Research Council, 1984) against amino acid requirements in grams per kilocalorie results in linear relationships (Table 6-1). Expression of amino acid and mineral requirements relative to energy density of the diet is useful because the energy level of the diet is important in controlling feed intake. It is assumed that without a change in the composition of gain, increased growth rates result in increased energy needs and thus increased feed intake. Use of these relationships to predict amino acid requirements for broilers growing at 10, 20, and 30 percent faster rates is shown in Table 6-2. A similar approach can be used to predict requirements for macrominerals at various fractional growth rates. Recommended diets based on corn and soybean meal for broiler chicks used in experiments with metabolic modifiers are shown in Table 6-3. Equations are based on the assumption that chicks are raised at thermoneutral environmental temperatures.

The use of empirically determined requirements from data across the growth period to predict requirements at augmented growth rates relies on several assumptions. First, this empirical approach assumes that the carcass composition of broilers given a metabolic modifier is similar to that of normal broilers at that part of their growth curve where they have the same fractional growth rate. Because normal broilers increase fat to lean ratios as they get older and their growth rates decrease, it follows that the regression approach assumes that a broiler that reaches market weight at a higher fractional growth rate is leaner than a normal broiler

TABLE 6-1 Regression Equations Used to Predict Nutrient Requirements (mg/kcal) for Broilers at Accelerated Growth Rates

Nutrient	Equation
Arginine	0.081 * FGR + 0.800
Glycine + serine	0.149 * FGR + 0.308
Histidine	0.017 * FGR + 0.219
Isoleucine	0.037 * FGR + 0.513
Leucine	0.064 * FGR + 0.850
Lysine	0.066 * FGR + 0.687
Methionine + cystine	0.062 * FGR + 0.437
Methionine	0.034 * FGR + 0.228
Phenylalanine + tyrosine	0.062 * FGR + 0.852
Phenylalanine	0.033 * FGR + 0.462
Threonine	0.022 * FGR + 0.628
Tryptophan	0.011 * FGR + 0.135
Valine	0.037 * FGR + 0.533
Calcium	0.037 * FGR + 0.713
Phosphorus (available)	0.018 * FGR + 0.307
Potassium	0.018 * FGR + 0.257

NOTE: Equations are derived by regressing requirements at 0 to 3, 3 to 6, and 6 to 8 weeks as estimated by the National Research Council (1984) on corresponding fractional growth rates (FGR) at each age. FGR expressed as percent per day used to derive equations were calculated from National Research Council (1984) data and are 7.96, 4.78, and 2.56 for 0 to 3, 3 to 6, and 6 to 8 weeks, respectively.

that reaches the same market weight at an older age. In practical terms, the amino acid requirements predicted by the regression equations assume that the carcass composition of female broilers growing at a 20 percent greater fractional rate have 18 percent less fat at the same market weight (2.2 kg) based on the fat accretion data of Hood (1982). As discussed above, many metabolic modifiers cause both a decrease in lipid accretion and an increase in protein accretion so that this assumption may be generally correct.

TABLE 6-2 Theoretical Percent of Nutrient Levels for Broiler Chicks, by Age (weeks), Growing at Normal and Augmented Rates

	Percent of the Diet											
	Normal			110% of normal			120% of normal			130% of normal		
Nutrient	0-3 weeks	3-6 weeks	6-8 weeks	0-3 weeks	3-6 weeks	6-8 weeks	0-3 weeks	3-6 weeks	6-8 weeks	0-3 weeks	3-6 weeks	6-8 weeks
Arginine	1.44	1.20	1.00	1.51	1.23	1.03	1.57	1.26	1.05	1.64	1.30	1.07
Glyine + serine	1.50	1.00	0.70	1.61	1.09	0.73	1.73	1.16	0.77	1.85	1.23	0.80
Histidine	0.35	0.30	0.26	0.37	0.31	0.27	0.38	0.32	0.27	0.39	0.32	0.28
Isoleucine	0.80	.070	0.60	0.84	0.71	0.62	0.87	0.73	0.63	0.90	0.74	0.64
Leucine	1.35	1.18	1.00	1.41	1.19	1.03	1.46	1.22	1.05	1.51	1.25	1.06
Lysine	1.20	1.00	0.85	1.27	1.04	0.88	1.33	1.09	0.92	1.37	1.11	0.93
Methionine + cystine	0.93	0.72	0.60	0.98	0.76	0.61	1.03	0.79	0.63	1.08	0.82	0.64
Methionine	0.50	0.38	0.32	0.53	0.41	0.32	0.55	0.42	0.33	0.58	0.44	0.34
Phenylalanine + tyrosine	1.34	1.17	1.00	1.40	1.18	1.03	1.44	1.21	1.04	1.49	1.24	1.06
Phenylalanine	0.72	0.63	0.54	0.75	0.64	0.56	0.78	0.65	0.56	0.80	0.67	0.57
Threonine	0.80	0.74	0.68	0.82	0.74	0.69	0.84	0.75	0.70	0.86	0.76	0.70
Tryptophan	0.23	0.18	0.17	0.24	0.19	0.17	0.24	0.20	0.18	0.25	0.21	0.17
Valine	0.82	0.72	0.62	0.86	0.73	0.64	0.89	0.75	0.65	0.92	0.76	0.66
Calcium	1.00	0.90	0.80	1.04	0.91	0.82	1.07	0.93	0.83	1.10	0.94	0.84
Phosphorus	0.45	0.40	0.35	0.46	0.40	0.36	0.48	0.41	0.36	0.49	0.42	0.37
Potassium	0.40	0.35	0.39	0.41	0.35	0.31	0.43	0.36	0.31	0.44	0.37	0.32

NOTE: Values are calculated from equations in Table 5-1 and assume that diets have a metabolizable energy level of 3,200 kcal/kg.

TABLE 6-3 Formulation of a Practical Reference Diet for Broiler Chicks Growing at 120 Percent of Normal Rates

	Percent of the Diet for Various Ages		
Ingredient	0-3 weeks	3-6 weeks	6-8 weeks
Ground corn[a]	50.48	61.89	69.39
Soybean meal[b]	38.96	29.92	24.01
Corn oil	6.22	4.45	3.27
Dicalcium phosphate	1.80	1.48	1.25
Limestone	1.50	1.37	1.28
Premix[c]	0.5	0.5	0.50
NaCl	0.25	0.25	0.26
DL-methionine	0.29	0.14	0.04

[a] Yellow corn with 8.8 percent protein.

[b] 48.5 percent protein.

[c] To supply the following per kg of diet: thiamin-HCl, 1.8 mg/kg; riboflavin, 3.6 mg/kg; calcium pantothenate, 10 mg/kg; niacin, 25 mg/kg; pyridoxin-HCl, 3 mg/kg; folate, 0.55 mg/kg; biotin, 0.15 mg/kg; vitamin B_{12}, 0.01 mg/kg; vitamin A, 1,500 IU/kg; vitamin D_3, 400 ICU/kg; vitamin E, 10 IU/kg; vitamin K, 0.55 mg/kg; antioxidant, 125 mg/kg; $MnSO_4 \cdot 5H_2O$, 170 mg/kg; $ZnSO_4$, 110 mg/kg; ferric citrate·5H $_2O$, 500 mg/kg; $CuSO_4 \cdot 5H_2O$, 16 mg/kg; Na_2SeO_3, 0.2 mg/kg.

Second, use of empirically derived requirements assumes that the relationship between amino acid requirements and growth rates is linear. Although this assumption is valid for birds with normal growth rates, it is not known whether the relationship holds at augmented rates.

Third, it is assumed that metabolic modifiers inducing augmented fractional growth rates do not change the proportion of amino acids required for maintenance relative to protein accretion. Certainly this assumption must be considered for each specific metabolic modifier because some are known to markedly affect the rate of amino acid catabolism (Chapter 2). Some anabolic hormones decrease rates of amino acid deamination and use for processes other than protein accretion. Consequently, use of values in Table 6-2 would tend to overestimate the amino acid requirement.

Few researchers have reported details on diets fed to experimental chicks exposed to metabolic modifiers. With a few notable exceptions, it is generally not clear if these diets meet accepted feeding standards such as NRC guidelines. Thus, it cannot be determined if adequate dietary amino acids were provided to permit improved growth rate or increased lean composition. Investigators are encouraged to publish descriptions of diets used in research on metabolic modifiers and use diets similar to those described here to assure that the diet does not limit the physiological expression of responses.

SUMMARY

Data demonstrating successful use of metabolic modifiers with poultry have not been sufficiently encouraging to stimulate development of products for market by pharmaceutical and allied industries. Only recently have recombinant chicken hormones become available, and there is a dearth of work with recombinant turkey hormones. It has also been speculated that the high reproductive capacity of poultry has permitted traditional breeding programs to optimize endogenous levels of anabolic hormones. Consequently, supplementation of additional hormone results in little augmentation of response. Alternately, it may be that our appreciation for the regulation of growth and lean tissue accretion gained using mammals is not relevant to poultry, and other classes of metabolic modifiers should be appraised for efficacy. In either case it is important that diets be used that permit the expression of increased growth and/or improved lean tissue accretion. Current knowledge of nutrient requirements versus growth rate of broilers indicate that diets that meet current NRC nutrient levels are not adequate for research on metabolic modifiers. Diets that will permit the expression of accelerated growth and lean tissue accretion require higher amino acid and macromineral levels in proportion to metabolizable energy content of the diet. Failure to use appropriate diets may prevent the realization of augmented gain and improved lean tissue accretion in experiments with metabolic modifiers.

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