

Growth Promotants — Promise, Problems and Perceptions

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Three issues stimulate our desire to alter growth of meat-producing animals: 1) a need to change the composition of meat animals and meat, 2) a need to reduce the return of nitrogen and other animal waste products to the environment, and 3) a need to increase the efficiency of animal growth to reduce use of natural resources and improve the sustainability of animal agriculture. All three impact directly on the producer, in one or more ways, and all three are achieved in part by the use of “growth promotants” or “metabolism modifiers”.

Our understanding of the linkages between human nutrition and health has expanded dramatically in the last fifteen years. Key nutritional concerns include level of fat and protein intake, proportion of fat intake as saturated fat, and cholesterol content of foods. One of the more recent issues involves the role of naturally-occurring antioxidants in foods and their role in prevention of certain cardiovascular diseases and cancers. This knowledge led to development of the “Dietary Guidelines,” the “Food Guide Pyramid” and expanded food labelling requirements. All were designed to help consumers make informed food choices at the point of purchase and to improve food consumption patterns.

Likewise, our understanding and application of new technologies, especially use of biotechnologies, in food production and manufacturing systems has expanded dramatically during this time. Chymosin that is produced by recombinant DNA technology is being used in cottage cheese manufacture. The genetically-altered Flavor-Saver® tomato was developed to markedly improve keeping qualities. The Food and Drug Administration (FDA) in 1993 approved the use of recombinantly-derived bovine somatotropin to improve efficiency of milk synthesis and lactation performance in dairy cattle in the U.S. Several other agronomic examples of use of biotechnology are in advanced stages of develop-

ment. Among them is the use of “growth promotants” or “metabolism modifiers” in meat animal species.

Although the “promise” offered by the use of many of these growth-enhancing technologies is significant, and even dramatic, they are not without problems or negative perceptions by consumers. Responses of contemporary consumers to use of biotechnology in food production and processing include increasing concern about the safety, nutritional value, quality characteristics and economic impact of these food commodities on traditional production systems. What are the promises, problems and perceptions of “growth promotants” and growth-enhancing technologies being developed for sustainable, environmentally friendly agricultural production systems?

Traditional management strategies currently employed in food animal production offer little opportunity for rapid improvement in composition of gain, feed efficiency or profitability. A major objective of discovery, development and application of molecular techniques and biotechnologies is to alter animal metabolism and partitioning of use of nutrients consumed toward increased rates of protein synthesis and deposition (i.e. muscle growth) and decreased rates of lipid synthesis and accretion. Changing composition of gain in this manner should concurrently improve efficiency of animal growth. The energetic cost of synthesizing and depositing a kilogram of protein is roughly equivalent to the energetic cost of synthesizing and depositing a kilogram of lipid. When protein is deposited in skeletal muscle, however, approximately 3.5 to 4 units of moisture are also accrued, making the energetic cost of muscle growth about one-fourth to one-third that required for an equal amount of adipose tissue growth in the finishing animal.

Some growth promotants or metabolism modifiers cause this dual-reciprocal change in composition of gain, and improve feed efficiency without changing feed intake, others may alter both and also change intake, while others may only influence either protein or lipid synthesis, with or without change in intake. It is useful to first define the classes of growth promotants or metabolism modifiers and then discuss the promises, problems and perceptions of their use.

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CLASSES OF GROWTH PROMOTANTS AND METABOLISM MODIFIERS

A working list of compounds would include compounds that have been approved for use in food-producing animals and those restricted to experimental investigation or currently under review by the FDA. Approved materials would include antimicrobials for use in livestock and poultry, ionophores and anabolic steroids approved for use in growing/finishing cattle. Those not approved include somatotropin (ST), natural somatotropin secretagogues such as growth hormone releasing factor (GRF), the hexapeptide His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂ (GHRP-6), or non-peptide ST secretagogues such as 3-amino-3-methyl-N-(2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-yl)(1,1'-biphenyl)-4-yl]methyl])-1H-1-benzapin-3-(R)-yl)-butamide (L692,429; Smith et al., 1993), and phenethanolamines or beta-adrenergic agonists.

PROMISES

Antibiotics

The list of antibiotics approved for use as growth enhancers in livestock and poultry is too long to include here, but includes bacitracins, bambamycin, lincomycin, penicillin, streptomycin, tetracyclines, tiamulin, tylosin and virginiamycin. Antimicrobials which are chemically synthesized and used in animal and poultry feeds include arsenicals (arsanilic acid, sodium arsenilate and roxarsone), sulfa drugs (sulfadimethoxine, sulfamethazine and sulfathiazole), carbadox and nitrofurans (furazolidone and nitrofurazone). The antibacterial ionophores will be described in the following section.

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

Effects of subtherapeutic use of antibiotics were documented as early as 1950. Efficacy in food-producing animals was summarized recently by Hays (1991). The data clearly show that effects in the very young animals are greater than in older animals, presumably because major benefits are achieved through inhibiting growth of bacteria that have adverse effects on growth. The more developed immune

system of older animals may be better able to protect the animal from the normal challenges encountered by exposure to these bacteria present in the environment. Conversely, effects are smaller when animals are exposed to environmental conditions which minimize exposure to pathogenic bacteria or which minimize stress and nutritional inadequacies.

Of the three possible modes of action, 1) disease control effects, 2) nutrient sparing effects and 3) metabolic effects, extensive evidence suggests that the major benefit from subtherapeutic use of antibiotics results from the control of harmful microorganisms. Early in the use of antibiotics in feed, it was noted that the magnitude of improvement in growth performance was inversely related to an animal's health status. Transport, intermingling of animals and environmental stress can result in exposure to non-resident microorganisms or a greater predisposition to subclinical disease. The use of subtherapeutic levels of antibiotics can reduce this stress and result in improved, more cost-efficient production. The bacteriostatic or bacteriocidal effects are apparent in contaminated or previously-used environments, where 5% to 10% improvements in growth rate or feed efficiency are commonly observed. Young animals in which the immune system is not yet fully developed also respond to a greater extent than older animals. Controlled experiments demonstrated that feeding antibiotics at subtherapeutic levels allow animals in these environments to perform closer to their genetic potential. Whether the effects are the result of decreased numbers of detrimental bacteria present or the result of reduction of toxic substances produced by the bacteria is uncertain.

Ionophores

An ionophore may be defined as an organic substance which binds a polar compound and acts as an ion transfer agent to facilitate movement of monovalent (sodium and potassium) and divalent ions (calcium) through cell membranes. The change in electrical charge in membranes influences transport of nutrients and metabolites across the cell membrane, but the exact mechanism by which ionophores improve growth performance in growing ruminants is not known. A recent review of the information available through 1990 describes the historical development, names and approved use guidelines, metabolism and statistically summarized efficacy of ionophores currently being used or studied (Owens et al., 1991).

The FDA first approved use of a polyether ionophore as a feed additive for cattle in 1975. Ionophores were first isolated from bacteria generally of the *Streptomyces* genus, but are produced commercially by bacterial fermentation. Monensin and other ionophores are now being fed to over 90% of feedlot cattle grown for beef. This wide use attests to the benefits of ionophore use in beef production. Ionophores are also used as anticoccidial drugs in poultry production, and have similar, but lesser effects in ruminants.

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

Ionophores consistently improve feed conversion efficiency in growing cattle. In many cases, feed intake is reduced without changing the rate of weight gain. When feed efficiency is improved, but intake is not changed, an increase in rate of weight gain is observed. Summaries of 228 trials in which monensin was fed indicated that gain-to-feed ratio was increased 4% to 12%, rate of gain was not significantly increased (1.6%), and feed intake was reduced 6.4%. Owens et al. (1991) regressed growth performance responses against monensin dose within each study for data compiled from published journal articles and experiment station publications up to 1990. Both linear and quadratic effects were observed, but in general, the magnitude of responses for rate and efficiency of gain was similar to values reported by Goodrich et al. (1984). Effects on carcass yield as a percentage of live weight and on carcass composition were very small, and in most cases not significant or of little economic importance. As expected, dietary administration of ionophores is coupled with the use of anabolic steroid implants to maximize rate and efficiency of gain in growing cattle. Effects of ionophores and anabolic steroid implants are generally additive.

Anabolic Steroids

Naturally-occurring and synthetic estrogens and androgens have been extensively and safely used to improve rates of gain, feed efficiency and carcass composition in growing beef cattle since the 1950's. A recent review of the biosynthesis, metabolism, names, approval dates, recommended doses, efficacy and mechanism of action of anabolic steroids is available (Hancock et al., 1991). Choice of commercial implant and re-implant strategies are targeted to gender-influences on efficacy, stage of growth, and the USDA Beef Quality grading system. Most implants have greater effect in younger cattle, increase feed intake by 5% to 10%, increase average daily gain (ADG) by 10% to 20%, and improve feed efficiency by 5% to 14%. Composition of gain is not markedly altered in cattle of varied genotype, particularly when cattle are fed to a constant carcass fat content endpoint (Perry et al., 1991). The live weight required to reach the "small degree of marbling" Quality grade criteria, however, was increased by 25 to 45 kg in steers administered a trenbolone acetate-estradiol combination implant. Estimates of economic impact of anabolic steroid implants indicate that savings associated with reduced feed costs are approximately \$50 per animal, and value of the carcass is increased by \$15 to \$30 per animal as the result of increased amount of saleable lean meat.

Somatotropin and Somatotropin Secretagogues

Unprecedented reduction (20% to 80%) in lipid deposition rates and 20% to 30% increases in skeletal muscle mass occur with exogenous administration of somatotropin (ST) in growing pigs. Exogenous administration of ST accelerates growth of several tissues through stimulating cell proliferation, accumulation of DNA and increased protein synthesis. The increases in circulating levels which result have independent effects on muscle and adipose tissue. Elevated levels repartition nutrient use toward greater rates of protein synthesis and deposition, and toward much reduced rates of lipogenesis and lipid accumulation in growing swine, sheep and cattle (see reviews by Hart and Johnson (1986); Beermann and DeVol (1991); Etherton and Smith (1991); Beermann (1994). Linear and quadratic dose-response relationships are present for most response variables (reduced feed intake, increased rate of gain, improved feed efficiency, and composition of gain), and different doses are required for individual specific response maxima. Responses are generally smaller in cattle and sheep than those observed in swine, but dose response relationships are present.

Exogenous ST administration increases ADG by up to 20% and reduces feed intake by up to 25% in pigs, resulting in even larger relative improvements in feed efficiency. Magnitude of response is dependent upon adequate nutrient availability, particularly amino acid balance and total amino acids available, when conventional cereal grain and soybean meal diets are fed. The improvement in efficiency of nitrogen use for growth appears to minimize any increase in protein requirement in young pigs up to 50 kg live weight, but a measurable increase has been observed during the finishing phases of pig growth.

Genotypic differences in growth performance and composition of gain are maintained across a wide range of ST dose in pigs, but gender differences are essentially eliminated. Gilts and barrows exhibit larger responses than intact males (boars) to make them equivalent at maximal response levels. These clear relationships have not been adequately documented in growing cattle and sheep.

Associated dose-dependent reductions in total lipid and saturated fatty acid concentration in adipose and skeletal muscle tissue derived from these animals is also observed, without any significant effects on cholesterol content or sensory characteristics (McKeith et al., 1994). A few studies have produced results that indicate reduced tenderness in loin chops from pigs administered high doses (100 to 200 $\mu\text{g}/\text{kg}$ live weight per day), but these are few. The possibility exists that genotype interactions are present which predispose some strains to reduced tenderness, compared with most that show no effect, even at high pST doses.

Because ST secretagogues achieve elevated circulating concentrations of ST, their efficacy is essentially equivalent. Because ST and GRF are peptides, both are administered by s.c. or i.m. injection. The action of GRF to stimulate ST secretion is short-lived (45 to 90 minutes), however, and it must be injected several times per day to achieve similar

efficacy. Less information is available regarding the long-term effects of the orally active ST secretagogues.

Phenethanolamines or Beta-Adrenergic Agonists

These compounds have been categorized as β -adrenergic agonists because they share structural and pharmacological properties with the endogenous catecholamines norepinephrine and epinephrine. Among the most extensively studied compounds are clenbuterol, cimaterol, ractopamine, L644-969, and salbutamol. These β -adrenergic agonists are orally active, and most have been shown to repartition nutrient use toward enhanced skeletal muscle growth (or protein deposition) and reduced lipid accretion. Broad generalizations regarding their efficacy and mode of action cannot be uniformly applied, however, because differences exist in responsiveness among mammalian and avian species, and among their dose-response relationships (see reviews by Williams, 1987, Moloney et al., 1991, Beermann, 1993, and Byrem et al., 1992). For example, clenbuterol, cimaterol and L-644,969 are particularly effective in growing ruminants (lambs and cattle) at doses of 1 to 10 ppm in the diet, whereas ractopamine is less effective at these doses and requires administration at doses of 20 to 80 ppm for maximal effect on growth or body composition. The basis for these differences is not entirely clear, but may be related to receptor specificity, pharmacokinetics or development of refractoriness with chronic administration.

Skeletal muscle mass is increased (15% to 40%) and lipid content of most adipose tissue depots is reduced (10% to 50%) in a dose-dependent manner, with little or no effect on bone. Increased rates and efficiency of live-weight gain are not consistently observed, and when present, are transient in some cases. Growth performance responses also depend upon the dose, treatment interval and overall effect on composition of gain.

PROBLEMS ASSOCIATED WITH USE OF GROWTH PROMOTANTS

Among the antibiotics and antimicrobials, the only serious problem appears to be failure of the producer to observe prescribed withdrawal periods. Residue levels are the major item of concern. Producers and production associations recognized the problem and took steps to increase educational efforts and participation in certification programs to avoid such occurrences. The issue of increased resistance of pathogenic microorganisms in response to chronic exposure to subtherapeutic levels of these drugs is still under investigation. At present, there are no indications that these levels pose any hazard to human health.

Use of anabolic steroids has few, if any associated problems. Implanting does require restraint of the animal, which can increase risk of injury, cause additional temporary stress, and requires additional labor as compared with not using them. The economic value of the carcass is an issue in that if rate of lipid deposition in the intramuscular adipose depot

is slowed, carcasses may not receive the "Choice" USDA Quality Grade designation for lack of marbling. This has been considered a "real" phenomenon when cattle are re-implanted with TBA-estradiol combined implants during the last 90 days before slaughter. As pointed out in the study by Perry et al. (1991), the live weight at which equivalent carcass fat content or degree of marbling may be increased by 25 to 45 kg. The increased rate of gain, feed efficiency and carcass weight attained with combined implant use during this phase of growth justifies their use, through the gain in economic value of the animal.

Neither somatotropin nor somatotropin secretagogues have been approved for use in growing animals in the U.S., although bST was approved for use in lactating dairy cows in 1993, and pST was approved for use in growing pigs in Australia in 1994. One response that may seem a negative is the reduced dressing percentage that occurs with use of ST. This result is explained by the fact that ST stimulates growth of the liver and kidneys, but not the gastrointestinal tract, and markedly reduces carcass adipose tissue mass, which leads to decreased percentage of live weight that is present in the carcass. A decrease of one or two percentage points is observed with moderate doses of pST, but again, the improved composition of the carcass overshadows this effect, and overall value of the animal is markedly enhanced.

Challenges for commercial use of pST or bST in growing animals include the delivery system. Because peptides would be digested in similar fashion to other proteins and peptides, they cannot be administered orally. Daily s.c. or i.m. injection requires daily restraint of the animal, and although some slow-release preparations have been developed, lesser effectiveness has been observed in pigs, lambs and cattle. The labor cost and physical effort required for daily administration is a deterrent to use. Another challenge, but not a problem, is the need for proper nutritional management of animals receiving ST. Inadequate energy and (or) amino acid supply will constrain responses. The reduced feed intake, and associated cost reductions, and increased value associated with increased carcass composition are the major incentives for use of ST in growing animals, but the economic incentive for use must also be present.

Producers also need to be aware that several factors influence incidence of ulcers in pigs. These include particle size or fineness of grind of diets, level of feed intake, genetic predisposition to elevated ulcer incidence, and pST administration at high doses. If two or three of these predisposing conditions are present, ulcer incidence could reduce growth performance or increase mortality. Higher incidence would be predicted with pST doses that maximize most responses (i.e. 200 μ g/kg body weight or equivalent), but the degree of interaction of all these factors has not been reported. Feed intake would be reduced the most at high doses, and if present in genotypes that are very efficient and also exhibit relatively low intakes, the problem could be exacerbated.

Because they are orally active, beta-agonists are easy to administer, but they need to be incorporated on a carrier,

because handling of the parent compound could result in inhalation during application, and amounts required are extremely small (2 to 20 ppm). Rapidity of response to some beta-agonists and subsequent down-regulation may be the reason that initial increases in ADG and feed efficiency are relatively short-lived, when compared with responses to anabolic steroids and ST. Again, generalizations for beta-agonists that alter composition of gain must be made with caution. Each is distinctly different in one or more aspects, and it now appears that only one, ractopamine, is currently under review by the FDA for approval in growing swine.

A good example of where one response phenomenon may not be present in all cases is the dose-dependent decrease in tenderness of meat from cattle and lambs fed beta-agonists other than ractopamine. This phenomenon is fairly consistent, both in magnitude and related physiological or biochemical changes in the calpain muscle proteinase system, whether fed or administered by direct arterial infusion (i.e. of cimaterol) in cattle. Ractopamine, however, has not been shown to cause any appreciable decline in tenderness of pork when fed at levels up to 20 ppm (McKeith et al., 1994). Composition of gain responses in swine also seem to be smaller than responses in sheep and cattle. Reasons for these differences are not readily apparent.

PERCEPTIONS

Perceptions held by consumers regarding use of growth promotants in meat animals and poultry range from indifference to keen criticism. The latter is often fueled by sensational cartoons and misinformation presented in the popular press and multimedia coverage of news releases. Sometimes too, lack of forthright and knowledgeable responses by producers to inquiries spawns skepticism and mistrust. I have experienced the misfortune of being quoted out of context on at least three occasions when interviewed about the efficacy, safety, ethics or impact on animal well-being of the use of metabolism modifiers. Many others have experienced similar serious challenges in hearings conducted on the efficacy and safety of bST in dairy cows.

Consumers need to be informed of the factual basis for the safety of use of growth promotants or metabolism modifiers. Whether they will be receptive or whether they will retain this information is not for us to judge. Rather, we need to teach the concepts of independent, objective scientific evaluation, which occurs at all levels of discovery, development, clinical and safety research and evaluation by the FDA and other Federal agencies. This is particularly difficult because consumers don't understand the scales of measurement that are used to monitor residue levels and metabolic changes. They cannot appreciate the fact that the presence of measurable levels in the parts per billion or less range are well below the established "safe" levels, and that there is no such entity as a "hormone-free" natural food. All edible plant and animal materials contain natural "hormone" or "growth factor" compounds. Marketing strategies that use terminologies such as "hormone-free", "drug-free", and "no additives"

do little to build consumer confidence in the safety of the myriad of "mainstream" foods that are available.

Consumers need to be informed about the nutritional contribution made by animal food products, the management strategies used to prevent negative ecological impact, the rationale for growth promotant use in modern production systems, and the economic contributions associated with use of these compounds toward improving the sustainability of animal agriculture. Accurate informational materials and media coverage of the advent of biotechnology applications in food production should be created and promoted, rather than shunned, by those directly involved in the research. This usually requires investigation, preparation and practice before a confident presence can be achieved in these endeavors. Familiarity with Federal regulations governing use of growth promotants, familiarity with evaluation, residue monitoring and surveillance procedures, familiarity with risk-benefit principles, and familiarity with effective communication skills are all needed to parlay our information into effective transmittal of "proper" perceptions being heard or developed by our audience.

If not challenged, inaccurate perceptions can become assumed fact, and too often the recipient has too little education in science to sift fiction from fact. Dramatic increases in the level of science education may be required of all consumers before accurate and adequate public awareness is achievable. Each of us is aware of the need to educate the public, but how many of us are adequately prepared and willing to invest the time to provide direct input? To borrow a quote from Dr. Harry Mersmann, "This condition will not change overnight, but doing nothing will only allow our condition to decline at an accelerating pace".

In summary, scientists in industry, academia and in Federal Agencies have a key role to play in educating consumers about technologies used in food production and processing, particularly in the use of growth promotants. The issue of food safety is almost always intertwined with consumer perceptions of the rationale for and "value" of production or management technologies. We need to be able and ready to provide the factual information needed to enlighten consumers regarding the scientific basis for adoption of these technologies, and provide them with an understanding of how political actions may sometimes be "misdirected."

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