Course PHA-3258(Drugs used for treatment of food producing animals)
By Prof .Dr/ Nehal Aly Afifi

The Ruminant Digestive System:
Other than the forestomachs (rumen, reticulum, omasum), the components of the ruminant GI tract are similar to those of monogastric mammals, and the use of pharmacologic agents to treat diseases of the glandular stomach (abomasum) and intestine follows principles common to both monogastric and ruminant species. Ruminants differ significantly from other mammals in that much of their feed undergoes microbial predigestion in the forestomachs, chiefly in the rumen and reticulum. There is also postgastric fermentation in the cecum and colon, but this is much less important than in some other herbivores, eg, horses.

Ruminoreticular motility or fermentation is depressed in many conditions, including improper feeding (overload or deficiency of specific nutrients), lack of water, infectious diseases, intoxications, lesions of any part of the upper GI tract, metabolic states (eg, hypocalcemia), or reduced flow of alkaline saliva that allows pH to fall and the microbial population to be altered to an extent that is harmful to the animal.

The primary objectives of pharmacotherapy are to remove the cause and to promote the return of normal digestive function by meeting or reestablishing the requirements for optimal ruminoreticular function as quickly as possible. This may include any of the following:
1) ensuring an appropriate substrate for microbial fermentation;
2) providing any cofactors (eg, phosphorus, sulfur) necessary for microbial fermentative processes;
3) removing any soluble end-products, undigested solid residues, and gas;
4) maintaining continual flow culture of ruminal microorganisms;
5) ensuring that the contents of the ruminoreticulum are fluid;
6) maintaining optimal intraruminal pH (generally between 6 and 7); and
7) promoting active ruminoreticular activity.

Drugs for Specific Purposes in the Ruminant Digestive System

1. <u>Esophageal Obstruction:</u>
Esophageal obstruction (choke) occurs when the esophagus is obstructed by food or foreign objects. It is the most common esophageal disease in large animals. Horses most commonly obstruct on grain, beet pulp, or hay. Esophageal obstruction can also occur after recovery from

standing chemical restraint or general anesthesia. Cattle tend to obstruct on a single solid object, eg, apples, beets, potatoes, turnips, corn stalks, or ears of corn.

Esophageal obstruction accompanied by ruminal tympani is an emergency, and if clinical signs of distress indicate, the bloat must be relieved by trocarization through the left sublumbar fossa.

Treatment: Esophageal obstruction in ruminants can be managed with standing esophageal lavage via orogastric tube or while under general anesthesia. Large foreign bodies can often be pushed into the rumen without further problems.

Esophageal obstruction due to a foreign body leads to severe discomfort and acute free-gas bloat. Physical removal of the object may be hampered by marked spasm of the surrounding muscle. Specific spasmolytic drugs such as acepromazine may be used (0.05–0.1 mg/kg, IV, IM, or SC in cattle). Alternatively, the moderate sedative and muscle relaxant effects of a low dose of xylazine (0.05 mg/kg, IM in cattle) or detomidine (0.02–0.05 mg/kg, IM in cattle) may aid removal of obstructions. None of these compounds has been approved by the FDA for use in cattle.

II. <u>Ruminotorics:</u>

Agents and mixtures that promote forestomach function (fermentation and motility) are known as ruminotorics. Formulations that contain glucogenic substrates, minerals, cofactors, and bitters (eg, nux vomica) have limited application in current therapy of ruminoreticular indigestion. Generally, restoration of the normal ruminoreticular environment using a physiologic approach is much more satisfactory.

Oral administration of specific alkalinizing or acidifying agents should not be routinely undertaken in cases of indigestion. Magnesium oxide or magnesium hydroxide are strongly alkalinizing agents able to substantially increase rumen pH and thus create a hostile environment for rumen protozoa. These compounds, when given at label dose to dairy cattle, result in significant decrease in rumen fermentation and a decrease in number of rumen protozoa. Therefore, these compounds should only be administered to cattle with a confirmed diagnosis of grain overload.

Mineral oil (1–2 L) or **dioctyl sodium sulfosuccinate** (DSS, 90–120 mL in 1–2 L of water) administered PO or via nasogastric tube followed by gentle ruminal massage can help promote the dissolution and passage of impacted fibrous ruminal omasal or abomasal contents. DSS can markedly depress rumen protozoa; thus, ruminal transfaunation should follow use of this agent if ruminal hypomotility continues.

III. Ruminal Fluid Transfer:

Fresh ruminal fluid is considered to be the best available “ruminotoric,” because it contains viable ruminal bacteria (1 × 10^8–10^{11}/mL) and protozoa (1 × 10^5–10^6/mL) as well as many useful fermentation factors (volatile fatty acids, microbial protein, minerals, vitamins, buffers). Strained fresh ruminal juice (at least 3 L, but 8–16 L is ideal in cattle; sheep require ~1 L) given PO or by tube is indicated in cases of ruminoreticular stasis. Ruminal fluid can be aspirated through a stomach tube from the ruminoreticulum of healthy animals using an extractor pump or by siphoning, or it can be collected at slaughterhouses. A rumen-cannulated donor animal is particularly convenient. It is best for the donor to be on a ration similar to that of the recipient, because the ruminal microflora will then be more appropriately adapted. Provided the initiating condition or lesion is responding favorably, improvement almost invariably follows the reestablishment of normal ruminal microflora, with consequent normalization of the fermentation process and ruminoreticular motility. When the ruminoreticular contents are putrified, ingesta must first be removed before transfer of fresh ruminal fluid. This can be accomplished using a large-bore stomach tube or by performing a rumenotomy. Acetic acid (vinegar, 4–10 L, PO) can be administered to cattle with putrefaction of the rumen associated with high rumen pH.

IV. Antifoaming Agents:

Therapeutic approaches to the control of acute frothy bloat involve administration of antifoaming agents to reduce foam stability and to promote release of free gas, which is then promptly eructated.

Bloat in Ruminants (Ruminal tympany):

Bloat is an overdistention of the rumenoreticulum with the gases of fermentation, either in the form of a persistent foam mixed with the ruminal contents, called primary or frothy bloat, or in the form of free gas separated from the ingesta, called secondary or free-gas bloat. It is predominantly a disorder of cattle but may also be seen in sheep. The susceptibility of individual cattle to bloat varies and is genetically determined.

Death rates as high as 20% are recorded in cattle grazing bloat-prone pasture, and in pastoral areas, the annual mortality rate from bloat in dairy cows may approach 1%. There is also economic loss from depressed milk production in nonfatal cases.. Bloat can be a significant cause of mortality in feedlot cattle.

Treatment: A trocar and cannula may be used for emergency relief, If the cannula fails to reduce the bloat , an emergency rumenotomy should be performed; it is accompanied by an explosive release of ruminal contents and, thus, marked relief for the cow. If the cannula provides some relief, an antifoaming agent can be administered through the cannula, which can remain in place until the animal has returned to normal, usually within several hours.

A variety of antifoaming agents are effective, including:

1. Vegetable oils (eg, peanut, corn, soybean) and mineral oils (paraffins).
2. Dioctyl sodium sulfosuccinate (docusate), a surfactant, is commonly incorporated into one of the above oils and sold as a proprietary antibloat , which is effective if administered early.
3. Poloxalene (25–50 g, PO) is effective in treating legume bloat but not feedlot bloat.

Placement of a rumen fistula provides short-term relief for cases of free-gas bloat associated with external obstruction of the esophagus. Available antifoaming agents include oils and fats and synthetic nonionic surfactants. Oils and fats are given at 60–120 mL/head/day; doses up to 240 mL are indicated during dangerous periods. Poloxalene, a synthetic polymer, is a highly effective nonionic surfactant that can be given at 10–20 g/head/day and up to 40 g/head/day in high-risk situations. It is safe and economical to use and is administered daily through the susceptible period by adding to water, feed grain mixtures, or molasses.

4. A similar polymer (Alfasure®) and a water soluble mixture of alcohol ethoxylate and pluronic detergents (Blocare 4511) also are effective.
5. Ionophores are effective in preventing bloat, and a sustained-release capsule that is administered into the rumen and releases 300 mg of monensin daily for a 100-day period protects against pasture bloat and improves milk production on bloat-prone pastures.

Acute frothy bloat in cattle should be treated with **poloxalene**, which administered as a drench or by stomach tube (25–50 g). Frothy bloat can be prevented by administering poloxalene as a top dressing to feed (1 g/45 kg body wt/day) or in a molasses block (1.5 g/45 kg body wt/day). **Polymerized methyl silicone** (3.3% emulsion [cattle: 30–60 mL; sheep: 7–15 mL]) is used in a similar manner as poloxalene, although direct intraruminal injection via a needle or cannula is more satisfactory in this case. Administration of docusate sodium in emulsified soybean oil (6–12 fl oz containing 240 mg/mL) or administration of vegetable oils alone, such as peanut oil, sunflower oil, or soybean oil (cattle: 60 mL; sheep: 10–15 mL), also relieves acute frothy bloat when given PO. The incidence of frothy bloat in feedlot cattle may be reduced by including ionophores (as monensin) either in the ration or administering as controlled-release capsules.

V. Ruminoreticular Antacids:

Ruminal alkalinizing agents are principally used to treat ruminal lactic acidosis (pH <5.5) due to grain engorgement or soluble carbohydrate overload. The resultant systemic dehydration and acidosis necessitate immediate correction of fluid and electrolyte balance and restoration of a viable microbial population. Often, the latter involves removal of ruminoreticular contents and replacement with fresh ruminoreticular fluid. Antacids that may be given PO, bid-tid, include magnesium hydroxide (cattle: 100–300 g; sheep: 10–30 g) and magnesium carbonate (cattle: 10–80 g; sheep: 1–8 g). Antacids should be mixed in ~10 L of warm water to ensure adequate dispersion through the ruminoreticular contents. Administration PO of activated charcoal (2 g/kg) is believed to protect the ruminoreticular mucosa from further injury by inactivating toxins. Oral administration of sodium bicarbonate (baking soda), either as powder dissolved in water or commercially available solutions prepared for IV infusion, rapidly neutralize the rumen pH but are accompanied by rapid release of large amounts of CO_2. Because of decreased rumen motility in ruminants with acute rumen acidosis, these animals are at increased risk of developing potentially life-threatening free gas bloat.

VI, Ruminoreticular Acidifying Agents:

Ruminal acidifying agents are used to treat ruminal stasis or simple indigestion as well as acute ammonia poisoning. In ruminal stasis, the intraruminal pH often increases to >7.5 because of the constant inflow of bicarbonate-rich saliva in the absence of active ruminal fermentation and formation of volatile fatty acids. In acute ammonia intoxication, the increased intraruminal pH increases the activity of urease and facilitates the absorption of free ammonia (pK_a of ammonium is 9.1). Administration of weak acids in cold water returns the pH of ruminoreticular content toward physiologic levels, promotes the uptake of volatile fatty acids, depresses the absorption of ammonia, and inhibits excessive urease activity. Acetic acid (4%–5%) or vinegar (cattle: 4–8 L; sheep: 250–500 mL) is the most common acidifying agent used.

VII. Modulators of Ruminoreticular Motility:

The use of motility modifiers in cattle is controversial, because evidence-based data demonstrating clinical efficacy are scarce. Several diseases, including paralytic ileus, cecal dilatation, and abomasal displacement, are accompanied by GI tract motility disorders. Pharmacologic motility modification may hasten recovery in some cases. However, in most instances, the most effective strategy to reestablish motility is correction of the underlying disorder (hypocalcemia, endotoxemia, alkalemia, obstruction, or organ displacement) followed by restoration of the normal ruminoreticular environment through transfaunation. Furthermore, conditioned responses to the presence of feed and feeding itself are physiologic means by which ruminoreticular motility can be notably enhanced.

Motility modifiers are categorized based on their mechanism of action. These can be cholinergics (parasympathomimetics), adrenergics, antidopaminergics, serotonergics, motilin agonists, opioid receptor blockers, or sodium channel blockers (lidocaine).

1. The use of parasympathomimetic agents (eg, neostigmine, physostigmine, bethanechol) is seldom appropriate. These drugs have cholinergic effects, which are potentially hazardous. **Neostigmine** (cattle: 0.02 mg/kg, SC; sheep: 0.01–0.02 mg/kg, SC) generally produces the fewest adverse effects but tends to increase frequency, rather than strength, of ruminoreticular contractions. Neostigmine given as a constant rate IV infusion (87.5 mg in 10 L of sodium-glucose infusion at 2 drops/sec) has been used to treat cecal dilatation/dislocation. However, the stimulatory effect of neostigmine is not always reliable, and some inhibition of motility can be seen. This may be due to the adrenergic component associated with ganglion stimulation by cholinergic agents.

Bethanechol (0.07 mg/kg, SC, tid for 2 days) has been used to treat spontaneous cecal dilatation without torsion. Potential adverse effects include salivation and diarrhea. Recommendations involving neostigmine and bethanechol have not been confirmed in randomized, controlled experiments. Neither compound has been approved by the FDA for use in cattle. Parasympathomimetics are sometimes used in practice to conservatively treat left displaced abomasum in cows, although the literature indicates that use of these compounds is of no value for this purpose.

N-butylscopolammonium bromide (nonlactating adult cattle: 0.2 mg/kg, IM or IV; calves: 0.4 mg/kg, IM or IV) is a parasympatholytic agent approved for the control of diarrhea in cattle in some European countries. The commercial formulation is combined with an NSAID, metamizole (nonlactating adult cattle: 25 mg/kg, IM or IV; calves: 50 mg/kg, IM or IV). Administration of N-butylscopolammonium bromide (80 mg/cow) in combination with dipyrone has been proposed as a conservative treatment of spontaneously occurring right-side displacement of the abomasum in cattle. N-butylscopolammonium bromide is not approved by the FDA, and the use of dipyrone in food animals in the USA is prohibited.

Atropine (0.04 mg/kg, IV) has been found to mitigate abomasal contractions for 1–3 hr. Atropine sulfate (0.5 mg/kg, IV) administered 5 min before placement of a reticular magnet is suggested to prevent magnet loss into the cranial sac of the rumen. Atropine (40 mg/cow as a 1% solution, SC) is also used to determine disruption of forestomach motility in cattle suspected to have vagal indigestion. An increase of >16% in heart rate 15 min after atropine administration is considered indicative of severe disruption of forestomach motility.

Xylazine hydrochloride (0.2 mg/kg, IV) administered 5 min before placement of a reticular magnet may prevent loss into the cranial sac of the rumen but will also result in deep sedation of the animal and thus is unlikely to be of any practical use. Xylazine-induced atony of the reticulorumen may be reversed by pretreatment with tolazoline (0.5 mg/kg, IV), atipamezole hydrochloride (0.08 mg/kg), or yohimbine (0.2 mg/kg, IV). Adverse effects of xylazine in cattle include bradycardia, hypothermia, salivation, diuresis, ruminal bloat, and aspiration pneumonia. Neither xylazine nor its antidotes have been approved by the FDA for use in cattle.

Metoclopramide (cattle: 0.15 mg/kg, IM; sheep: 0.023–0.045 mg/kg) has cholinergic and antidopaminergic effects but does not appear to increase the myoelectric activity of the pyloric antrum in either species. However, metoclopramide at 0.5 mg/kg given IM or IV to goats has been shown to increase myoelectric activity of the pyloric antrum but not the body of the abomasum. Because metoclopramide can cross the blood-brain barrier, restlessness and excitement are potential adverse effects. Metoclopramide has not been approved by the FDA for use in cattle.

Erythromycin lactobionate is a macrolide antimicrobial that increases gut myoelectric activity by binding to motilin receptors in intestinal smooth muscle cells. In cows, erythromycin (0.1 mg/kg, IV, or 1 mg/kg, IM) was found to increase myoelectrical activity in the abomasum and duodenum for >2 hr. This effect was increased to 6–8 hr when erythromycin was administered in polyethylene glycol at 10 mg/kg, IM. Erythromycin is approved by the FDA only for treatment of shipping fever, pneumonia, foot rot, and metritis at 2.2 mg/kg, IM. Deep IM injection in muscles of the neck is recommended because of the risk of pain, swelling, and tissue blemishes at the injection site.

The prokinetic serotoninergic drug cisapride (cattle: 0.08 mg/kg) is widely used in equine medicine, yet significant prokinetic effects have not been conclusively demonstrated in ruminants.

VIII. Drug Disposition in the Ruminoreticulum:

Morphologic and functional characteristics of the ruminoreticulum that make it suitable for fermentative digestion of plant material also affect the activity, distribution, and absorption of many drugs, particularly when given PO. The anaerobic and reductive environment of the ruminoreticulum and the presence of many microbial enzymes result in inactivation of drugs such as trimethoprim and cardiac glycosides. Slow and inefficient mixing of drugs in the large volume of the ruminoreticular fluid delays attainment of uniform concentrations throughout the multiphasic ingesta and retards absorption from the ruminoreticulum. Absorption is also affected by the polarity and ionization status of the drug, which is determined by the pK_a of the drug and the pH of the ruminoreticular fluid. The latter depends on the diet and the relative contributions of alkaline saliva and acidic ruminoreticular fluid. Aside from the many effects that the ruminoreticular environment can have on the activity and disposition of drugs, the drugs themselves may have unintended effects on ruminoreticular function. In particular, broad-spectrum antibacterial agents and antiprotozoal agents can disrupt the normal balance of microflora in the ruminoreticulum.

These factors affecting the activity and disposition of drugs in the ruminoreticulum, together with the possible effects of drugs on ruminoreticular function, complicate oral administration of drugs to ruminants. In young animals, these undesirable effects can be avoided by making use of the esophageal groove reflex. This reflex, which is elicited by receptors in the mouth and pharynx, is well developed in suckling neonates but becomes less reliable in older animals. After ~24 mo in cattle and ~18 mo in sheep, provoked reticular groove closure is often irregular, incomplete, or absent.

Ruminoreticular morphology and function has less influence on drug disposition in neonatal ruminants than in adults. At birth, the forestomachs are underdeveloped, and the newborn ruminant is essentially monogastric. Drugs that are usually destroyed in the ruminoreticulum of adults (eg, trimethoprim) may be well absorbed during the first 2–3 wk of life. This developmental pattern depends on the period between birth and initiation of a roughage diet and exposure to microbes in the environment.

Growth Promotants and Production Enhancers

Overview of Growth Promotants and Production Enhancers:

Achieving increased efficiency of feed conversion into edible human food products of high quality, without posing any significant risk to the consumer, is an important goal of livestock producers worldwide. The physiologic mechanisms involved in converting feed into muscle, fat, and bone by animals are increasingly being elucidated. Recently, consumer concerns about additives for food production have focused on animal safety, organoleptic quality, and the potential human health hazards of the food we eat.
A number of approaches may be taken to improve conversion of animal feed into meat; two of the more practical approaches are hormonal treatments and antimicrobial feed additives. The hormonal approach includes administration of anabolic steroid hormones, use of growth hormone (GH) or insulin-like growth factor (IGF-1) to augment endogenous GH levels, and use of β-adrenergic agonists (βAAs) to preferentially increase nutrient partitioning to muscle . The antimicrobial feed additives approach includes feeding of antibiotics to decrease populations of pathologic bacteria in host GI tracts, use of compounds to manipulate ruminal fermentation by

changing the ruminal microflora population in healthy animals, and use of probiotics to promote beneficial microflora in the GI tract.

The use of hormonal treatments and antimicrobial feed additives in production animals is currently under debate in many areas and is banned in some because of concerns surrounding their possible effects on people.

More recently, use of βAAs for growth promotion in swine and beef production has come under scrutiny in the international meat trade community. Some countries, including the EU, Russia, and China, have placed a total ban on beef and pork from nations that allow the use of βAAs, whereas other countries have adopted the maximum residue limits (MRLs) for the compounds as established by the Codex Alimentarius Commission. The FDA applies a higher MRL in the USA than the Codex standard.

The use of antimicrobial compounds specifically for growth-promotion purposes, as opposed to their use for control or treatment of bacterial infection, has also come under increased attention internationally because of rising concerns over antimicrobial resistance by pathogenic bacteria of concern in human medicine. Direct cause-effect evidence of antimicrobial use in livestock leading to bacterial resistance in human medicine is virtually nonexistent, requiring more complicated epidemiologic study. However, numerous studies have linked use of specific drugs in livestock, either for disease therapy or for growth-promotion purposes, to increased prevalence of drug resistance in target bacterial species. Results of these investigations are equivocal and have been the focal point of intense scrutiny and debate. In the absence of resoundingly clear cause-and-effect data, and because preservation of the continued efficacy of existing antimicrobial compounds is paramount, the cautionary principle has prevailed and will likely lead to greater restrictions on the use of antimicrobials for growth promotion in livestock and for therapeutic purposes as well.

Steroid Hormones:

In general, the principle that dictates which type of hormone to be used is the need to supplement or replace the particular hormone type that is deficient in the animals to be treated. Females produce estrogens normally, so better results are obtained from the administration of male androgens, eg, trenbolone acetate (TBA). Estrogens should not be used in animals to be retained for breeding purposes. Manufacturers' instructions must be followed to ensure proper implant placement and dose administration. Anabolic hormones should not be administered by IM injection for growth-promoting purposes. Additionally, steroid hormones must not be used for anabolic or other purposes unless the indication is specifically approved by the appropriate regulatory body. The EU has banned the use of hormonal growth promoters in meat production. Appropriate surveillance programs have been established to ensure compliance by producers.

1. **ENDOGENOUS STEROIDS**

The steroidal compounds used for anabolic purposes in food animals are estradiol, progesterone, and testosterone. Gender and maturity of an animal influence its growth rate and body composition. Bulls grow 8%–12% faster than steers, have better feed efficiencies, and produce leaner carcasses. Superior performance of bulls is due to the steroids produced in the testes (mainly testosterone but also estradiol, which in ruminants is also anabolic and is produced in relatively large quantities). Testosterone, or one of its physiologically active metabolites, binds to receptors in muscle and stimulates increased incorporation of amino acids into protein, thereby increasing muscle mass without a concomitant increase in adipose tissue. Estradiol, on the other hand, may act by stimulation of the somatotropic axis to increase growth hormone and thus IGF-1 production and availability by modulation of the IGF binding proteins. Naturally produced endogenous steroids are not orally active, require picogram concentrations of estradiol and nanogram concentrations of testosterone in blood for physiologic effects, and can transiently affect the behavior of treated animals.

Table 1

Natural Steroid Hormones for Consideration as Growth Promoters

Hormone	Form[a]	Dosage	Duration of Effect (days)	Growth Response	Potential Adverse Effects
Estradiol	1 - Pellet	20 mg EB[b] + 200 mg P4[c] (steers)	100–120	10%–15%	Transient increase in sexual behavior
Estradiol	2 - Pellet	20 mg EB + 200 mg testosterone propionate	100–120	5%–15%	Udder development
Estradiol	3 - Pellet	10 mg EB + 100 mg P4 (veal calves)	100–120	0–8%	
Estradiol	4 - Silastic rubber	45 mg estradiol (steers)	365	10%–15%	Transient increase in sexual behavior
Estradiol	5 - Silastic rubber	24 mg estradiol (steers)	200	10%–15%	Transient increase in sexual behavior

Estradiol	6 - Polylactic acid	28 mg estradiol (steers)	365	10%–15%	Transient increase in sexual behavior
Progesterone	*See* 1& 3				
Testosterone	*See* 2				

[a] Implants must be placed SC between the ear cartilage and skin to comply with label instructions so that consumption of residues may be avoided.

[b] Estradiol benzoate

[c] Progesterone

Estradiol

A potent anabolic agent in ruminants at blood concentrations of 5–100 pg/mL, estradiol is administered as an ear implant, either as compressed tablets or silastic rubber implants. When estradiol is formulated as compressed tablets, a second steroid (usually testosterone or progesterone) is typically present when administered to feedlot cattle fed a high-energy diet, in a ratio of ~1 part estradiol to either 5 or 10 parts of the other, androgenic, steroid. The release of hormones from compressed pellets is biphasic, with a relatively rapid rate lasting 2–7 days after insertion (50–100 times higher than baseline), followed by a slower rate of release for the next 30–100 days (5–10 times higher than baseline). Hormone concentrations gradually decline up to day 80–100, when concentrations are no different from those in control animals.

Estradiol formulated in silastic rubber enhances the effective life span of the implant relative to pelleted formulations. The pattern of release includes a short-lived spike in plasma estrogen concentration for 2–5 days after insertion, followed by a stable but modest increase (5–10 times greater than baseline). Toward the end of the effective life span of the implant, there is a gradual decline to estradial concentrations found in control animals.

Estradiol, on its own, increases nitrogen retention, growth rate by 10%–20% in steers, lean meat content by 1%–3%, and feed efficiency by 5%–8%. It can be used in steers to best advantage, but it has some anabolic effects in heifers and veal calves. It works best in lambs in conjunction with androgens. It is not effective as an anabolic agent in pigs.

Testosterone

A potent anabolic agent at the relatively high concentrations of 1–5 ng/mL in peripheral circulation, testosterone is not used on its own as an anabolic agent in farm animals, because it is very difficult to achieve the effective physiologic concentrations for long periods (up to 100 days) with current delivery systems. It is generally used as a propionate formulation in conjunction with 20 mg estradiol benzoate (EB) in a compressed tablet implant; its major role in the compressed pellet may be to slow down the release rate of estradiol. In high concentrations in blood, testosterone induces male sexual behavior (eg, aggression and mounting), but this is not seen with the concentrations delivered by compressed pellets in the ear (1 ng/mL). Behavior resulting from use of 20 mg EB and 200 mg progesterone is not different from that seen after the use of 20 mg EB and 200 mg testosterone propionate.

Progesterone

Unambiguous data suggesting progesterone is anabolic in farm animals does not exist. Its major use is to slow the release of estradiol from compressed pellet implants.

2. SYNTHETIC STEROIDS

Synthetic steroids are commercially available in some countries because of their efficacy, their relatively mild androgenicity, and because they cause few behavioral anomalies .Commercial synthetic steroids are androgenic (TBA) or progestogenic (melengestrol acetate, MGA).

Table 2

Synthetic Steroid Hormones for Consideration as Growth Promoters [a]

Hormone	Method of Administration	Dosage	Duration of Effect (days)	Growth Response	Potential Adverse Effects
TBA	Pellet implant	200 mg	60–90	5%–12%	
TBA + EB	Pellet implant	200 mg TBA + 28 mg EB	90–120	10%–20%	Transient increase in sexual behavior
		100 mg TBA + 14 mg EB	90–120	10%–20%	Transient increase in sexual behavior
TBA + E	Pellet implant	200 mg TBA + 20 mg E	90–120		
		120 mg TBA + 24 mg E	90–120		

		140 mg TBA + 14 mg E	90–120		
		80 mg TBA + 16 mg E	90–120		
		80 mg TBA + 8 mg E	90–120		
		40 mg TBA + 8 mg E	90–120		
TBA + E	Pellet implant	200 mg TBA + 40 mg E	200		
Zeranol	Pellet implant	36 mg zeranol	90–120	10%–15%	
		12 mg zeranol	90–120	10%–15%	
MGA	In feed	0.25–0.5 mg/day, PO	As long as it is given	3%–10%	Increased mammary developme nt after long-term administrati o

[a] TBA = trenbolone acetate; EB = estradiol benzoate; E = estradiol 17β; MGA = melengestrol acetate

Synthetic steroidal androgens are not commonly used as anabolic agents except for TBA. TBA is currently the only synthetic androgen approved for use for growth promotion in cattle; it is used to a lesser extent in sheep and not in pigs or horses. It has weak androgenic activity but has greater anabolic activity than testosterone. When administered repeatedly during the feedlot phase when cattle are fed a high-energy diet, TBA can alter the physical appearance and behavior of steers, causing them to look and act like bulls. **TBA** has significant anabolic effects on its own in female cattle and sheep, but in castrated males it gives maximal response when used in conjunction with estrogens. It is administered as a pellet-type implant containing

140–200 mg TBA for heifers and cull cows, and it can be used with estradiol in doses ranging from 140–200 mg TBA as either combined or separate implants.

Melengestrol acetate (MGA) is an orally active synthetic progestagen. It is fed at dosages of 0.25–0.5 mg/day per heifer in the feed. It suppresses recurrent estrus in feedlot heifers and increases growth rate and feed efficiency. It is not effective in pregnant or spayed heifers or in steers. Its mode of action is to suppress ovulation, presumably by suppressing luteinizing hormone (LH) pulse frequency; however, large follicles develop, which can increase concentrations of estradiol and growth hormone, and hence growth. MGA is permitted for use in the USA but not in the EU. When used in the absence of a growth-promoting implant, MGA increases growth rate through the increased estradiol released by the follicles; however, when used in conjunction with either estradiol or combination estradiol/TBA implants in the feedlot, the growth-promoting benefits of MGA are primarily derived from suppression of the excess, unproductive, and potentially harmful activities associated with recurrent estrus.

3. SYNTHETIC NONSTEROIDAL ESTROGENS

Two major classes of synthetic nonsteroidal estrogens have been used as production enhancers in food animals. **Stilbene estrogens** (either diethylstilbestrol [DES] or hexestrol) have been banned in most countries as anabolic agents because of residue and food safety concerns. The discovery of a naturally occurring estrogen, zearalenone (produced by the fungi *Fusarium* spp), led to the development of the synthetic analog zeranol. **Zeranol** is estrogenic and has a weak affinity for the uterine estradiol receptor. It is used in animal production as a SC ear implant at a dose of 36 mg for cattle and 12 mg for sheep, with a duration of activity of 90–120 days. In steers, zeranol increases nitrogen retention, growth rate by 12%–15%, and feed conversion by 6%–10%. However, lower responses are seen in heifers. Its effects are additive to those of androgens (generally TBA).

USE IN CATTLE:

Calves have a high conversion of feed into animal tissue compared with young growing swine or poultry. Therefore, their responses to anabolic agents are variable. Responses of 0–10% have been obtained when zeranol was given to 3-mo-old castrated male calves. Bull calves in an intensive bull beef system can be given an estrogen implant at 1–2 mo of age to suppress testicular development, which may lead to subsequent reduction in mounting and aggression. A growth response of ~5%–8% is also obtained from this implant. Reimplantation every 80–100 days is necessary if compressed pellet implants are used.

A major limitation to the use of anabolic agents in lightweight weaned calves is the low liveweight gain they may achieve because of poor nutritional status. Hence, anabolic agents should be considered only if the weanlings are expected to gain >0.25 kg/day. Zeranol, estradiol, and TBA can be used in male castrates. Dairy heifer replacements cannot be given steroid implants as weanlings.

Higher and more consistent responses are obtained in yearling and older cattle than in calves or weanlings, due primarily to greater intake and to the higher plane of nutrition. In the case of pellet-type implants with effectiveness of 90–120 days, consideration can be given to reimplanting cattle midway through the grazing season, provided gains >0.5 kg/day are maintained. Silastic implants of estradiol are effective for 200–400 days, depending on dose used. Daily gains in feedlot cattle fed a high-energy diet may be increased 20%–30% after implantation with an estrogen and an androgen; daily gain in pasture cattle is typically improved by 10%–15%.

Responses to growth promotion are good when animals are on a high plane of nutrition. Feed conversion efficiency is improved, and lean meat content of the carcass is generally increased. Although less clear, conformation of implanted cattle tends to improve. Negative impacts of implants on marbling content of the loin muscle can be minimized by finishing cattle to a fat-constant endpoint.

In steers and heifers in the feedlot and provided a high-energy diet, use of an androgen plus an estrogen hormone combination is common. Pellet-type implants are effective for as long as 150 days; reimplanting cattle after 70–100 days should be considered because of decreasing response from the pellet-type implants over time.

Results from large-pen studies (>25 animals/pen) show that heifers benefit from a combination of estradiol, TBA, and MGA. In small-pen research, however, when fed in combination with growth-promoting implants, MGA use results in reduced gain, feed efficiency, and ribeye area, as well as increased fatness. These contrary findings suggest that although progesterone may have an “anti-growth promoting” effect, the growth-promotion benefit realized from suppression of estrus overcomes the minor negative physiologic impact of progesterone in conventional large feedlot pens.

In some studies in which bulls were treated with estrogens, growth rate increased by 2%–10%, and testicular growth was suppressed with a subsequent reduction in mounting and aggression. This should make the bulls easier to manage on the farm and less subject to “dark cutting” after slaughter. The mechanism involved appears to be the reduction of the gonadotropic hormones LH and follicle-stimulating hormone (FSH) from the pituitary gland by estrogen, which has a strong negative feedback effect on LH and FSH secretion. This reduction in LH and FSH results in decreased testicular size and lower testosterone levels, with a consequent reduction in aggressive behavior. However, there appears to be sufficient testosterone secreted to maintain an anabolic effect. Therefore, the repeated use of estrogens in bulls beginning at 1–3 mo of age may lead to a hormonal castration effect with increased growth rate.

.**USE IN OTHER SPECIES:**

In **pigs**, the growth responses from the use of estradiol, progesterone, and zeranol are variable but generally low. TBA seems to increase lean meat content of pig carcasses.

In **sheep**, the responses to anabolic agents parallel those obtained in cattle. The most consistent responses have been obtained in lambs finished on high-concentrate diets; a 10%–15% increase in daily gain can be expected. Anabolic steroids should not be used in lambs to be retained for breeding. Also, implantation with zeranol reduces testicular development in ram lambs and delays the onset of puberty and reduces the ovulation rate in female sheep. Moreover, the short finishing period and the extensive nature of some production systems militate against widespread practical use of growth promotants in sheep on economic grounds.

In **poultry**, responses to estrogens include increased fat deposition. Androgens, however, have given conflicting responses. Hence, their use is of no practical significance at this time.

In **fish**, methyl testosterone can induce sex reversal in rainbow trout, thereby promoting growth and improved feed conversion efficiency.

POSSIBLE COMPLICATIONS:

Any hormonal implant has a negative feedback effect on pituitary gonadotropins, thereby reducing LH and FSH secretion. Therefore, they can affect the onset of puberty and the regularity of estrous cycles, as well as reduce conception rate in females and testicular development (and thus sperm output) in males. Hormonal growth promotants should never be used in animals that are or may be used for breeding purposes; nor should they be used before puberty to increase growth in yearling thoroughbreds or young pedigree bulls for show purposes. If given to pregnant heifers, TBA results in increased incidence of severe dystocia, masculinization of female genitalia of the fetus, increased calf mortality, and reduced milk yield in the subsequent lactation.

The major problem thought to be associated with estrogenic implant use in the feedyard has been a transient increase in mounting behavior and aggression, commonly referred to as buller syndrome. However, it is also believed that the estrogen in the implant alone is not sufficient to cause bullers. Buller syndrome generally affects 2%–3% of the feedyard steer population, but this rate can double or triple during the late summer and early fall months. An increase in yearling steers off native grass pasture (which are usually given a high-dose implant immediately on arrival), diurnal temperature fluctuations (hot days and cool nights that shift social activity to early evening hours), dusty pen conditions (exacerbated by evening social activity), feeding corn or hay that may be moldy, and incomplete fermentation on freshly harvested silage can also contribute to increases in buller syndrome. These effects generally last for 1–10 days after implantation and then subside. However, there have been a few reports of undesirable behavior in steers that lasted for 4–10 wk. The cause of this unpredictable adverse behavior is not clear; it may be a function of rearing and socialization climate. It is generally more severe in dairy cattle used for beef production. If the problem is severe, the buller steers should be identified and removed; if very severe, removal of the implants or administration of 50–100 mg of progesterone in oil for a number of days to suppress behavior should be considered.

In addition to buller syndrome, estrogenic implants may increase the size of rudimentary teats.

Growth Hormone:

The peptide most commonly used to enhance growth and production is growth hormone (GH). Its chemical structure is species-specific and it has a short half-life (20–30 min). It is not orally active and is rapidly digested and cleared by the gut, liver, and kidney; thus, it must be administered via a parenteral route. Sustained-release (14–28 days) formulations have been developed for use in cattle to obviate the need for daily injections. When administered to cattle, GH increases growth rate (5%–10%), feed conversion efficiency, and the carcass lean:fat ratio. Gender has little effect on response in cattle. Response to GH is lower in older cattle with greater fat deposition. There is an interaction between magnitude of response and nutritional level; protein content and specific amino acid composition may be important to achieve maximal responses. The effects of GH are largely additive to those obtained from steroid implants. GH improves growth and feed efficiency in sheep but not in poultry. Recombinant GH in pigs has dramatic effects, resulting in an increase in daily gain (20%), decrease in feed intake (5%), and a decrease in the feed:gain ratio (20%). A 10% increase in lean content and a 35% decrease in adipose tissue may be realized in swine. Administration of bovine GH at 25 mg/day to lactating cattle increases milk yields of dairy cows by as much as 20%. GH has been approved for commercial use in some countries to increase milk production.

β-Adrenergic Agonists

β-Adrenoceptor agonists are catecholamines and are chemically similar in structure to noradrenaline and have neurotransmitter, paracrine, and endocrine effects. They bind to specific β-receptor (β_1 or β_2) and increase intracellular c-AMP levels resulting in increasing growth rate, improve feed efficiency and lean-meat content of beef cattle, sheep, pigs and poultry.

The characteristics of β-adrenoceptor agonists depend on:

1- Relative binding to β2-receptors (**Clenbuterol** and **Cimateratol**).
2- Specificity of binding in target tissues likes adipocytes **(L-540.000)**.
3- Percentage occupancy of receptors.

4- Efficacy of the analogue at the β-adrenoceptor.

The mechanism of action of β-Adrenoceptor agonists involves some or all of the following:

1- Increase in muscle accretion.
2- Decreased lipogenesis after binding to adipose tissue receptor
3- Marked decrease in insulin.
4- Increased the blood flow to the hind limb and to adipocytes

Antimicrobial Feed Additives

Maintenance of healthy animals requires prevention of infection by pathogenic organisms. In addition, specific alteration of a host's microflora may have beneficial effects on animal production by alteration of ruminal flora, resulting in changes in the proportions of volatile fatty acids produced during ruminal digestion. Thus, antimicrobial compounds may improve production efficiency of healthy animals fed optimal nutritional regimens. Production-enhancing antimicrobial compounds can be classified as ionophore or nonionophore antibiotics. This distinction is important, because ionophores have no use in human medicine and do not have any link or possible effect on antimicrobial resistance to therapeutic antibiotics in either people or food animals; to group all antimicrobials together for debate about the risk to therapeutic antibiotics is ill advised and overly simplistic. Antimicrobial compounds are administered in the feed at low dose rates relative to high doses required for therapeutic effects. Feed additives can be given once the rumen is functioning, although some antibiotic compounds can be fed to calves before this point.

Antimicrobial growth promotants commonly used in livestock are detailed in Table 3:. Antimicrobials are used in male and female animals without adverse effects on ovarian and testicular development or function because they are poorly absorbed. Unlike anabolic steroids, they do not affect carcass composition. Antimicrobials are commonly used in conjunction with estradiol, zeranol, or TBA, and generally their combined effects are additive.

1. IONOPHORE ANTIBIOTICS

Ionophores (eg, monensin and lasalocid) modify the movement of monovalent (sodium and potassium) and divalent (calcium) ions across biologic membranes, modify the rumen microflora, decrease acetate and methane production, increase propionate, may improve nitrogen utilization, and can increase dry matter digestibility in ruminants. Their main effect is to increase feed efficiency, but they may also improve growth rates of ruminants on high-roughage diets. Administration of monensin to cattle results in 2%–10% improvement in liveweight gain (in animals on a high-roughage diet), 3%–7% increase in feed conversion efficiency, and up to a 6% decrease in food consumption.

Initially, monensin was used only as a feed additive for ruminants fed in confinement, but its use has been extended to grazing animals. Other ionophores generally have similar effects. Doses range from 6–40 ppm in the diet. Ionophores are absorbed from the gut, rapidly metabolized by the liver, and reenter the gut from bile. Some ionophores also have a therapeutic use (eg, for prevention of coccidiosis in ruminants and poultry).

Table 3

Antibacterial Growth Promoters for Potential Use in Livestock Production

Compound	Class	Absorption	Effects
Bambermycins	Phosphoglycolipid	Not absorbed	Increase FCE[a], growth promotion in poultry, cattle
Lasalocid sodium	Ionophore		Increase FCE in cattle
Monensin sodium	Ionophore	Poorly absorbed	Increase FCE, increase DLWG[b] in cattle and lambs
Salinomycin	Ionophore		Increase DLWG and FCE
Virginiamycin	Peptide	Not absorbed	Growth promotion in poultry
Zinc bacitracin	Peptide	Not absorbed	Growth promotion in poultry

[a] Feed conversion efficiency

[b] Daily liveweight gain

2. NONIONOPHORE ANTIBIOTICS

These compounds are used to selectively modify microbial populations within animals to improve production efficiency and to maintain health by combating low-level infections, particularly in intensive systems. Phosphoglycolipid antibiotics (eg, flavophospholipol) alter ruminal flora by inhibiting the action of some gram-positive gut microorganisms and peptoglycan formation, yielding similar production responses to those produced by ionophores. In addition, flavophospholipol has been shown to influence the hindgut microflora populations, resulting in competitive exclusion of some harmful pathogens such as *Escherichia coli* and various species of *Salmonella*. A less understood effect of flavophospholipol is the reduction in plasmid transfer of antimicrobial resistance. Given the seemingly contradictory and highly charged interests of desire for a generalized reduction in the use of antibiotics for livestock production and the potential use of a specific antibiotic for reducing antimicrobial resistance, this potentially volatile topic has not been comprehensively assessed.

The means by which specific compounds exert their antimicrobial effect differ. Antibiotics may have a nitrogen-sparing effect, thereby increasing the availability of amino acids to the animal.

Most feeds for broiler and pig production in some countries contain antimicrobial growth promoters. These compounds can also be administered to calves, yearlings, and finishing cattle either in milk replacer or in supplementary concentrates. Antibiotic compounds, in general, increase growth rate by 2%–10% and feed conversion efficiency by 3%–9%. Their effects are greater in young animals, and production responses are reduced when production conditions are optimized (good housing, optimal health, and hygiene). They have minimal effects on carcass composition other than that because of improved growth rate.

The development of microbial resistance to antibiotics in treated animals, which can then be spread to people, is an important concern regarding the widespread use of antimicrobial feed additives in food production. There is circumstantial evidence that use of subtherapeutic doses of antimicrobials creates selective pressure for the emergence of antimicrobial resistance, which may be transmitted to the consumer from food or through contact with treated animals or animal manure. A ban on the use of antibiotics as feed additives decreased drug-resistant bacteria in a Danish study. While overall mortality rates of chickens were not affected, more feed was consumed per kg of weight. Therapeutic use of antibiotics was increased, but the total volume of antibiotic use was significantly decreased. The EU has banned bacitracin, carbodox, olaquindox, tylosin, virginiamycin, avilamycin, flavophospholipol, lasalocid sodium, monensin sodium, and salinomycin as of 2009. There has been no reported evidence of any reduction in antimicrobial resistance in human bacterial pathogens as a result of the EU ban. This is understandable given that the most important and concerning cases of antimicrobial resistance in human medicine, namely methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), *Streptococcus pneumoniae*, and others, are not food-borne pathogens, are not found in food or companion animals, and the drugs of interest are not used and were not used before the ban in livestock. The issue of antimicrobial resistance is critical for the immediate and long-term future of human medicine; however, the complexity of the issue and the difficulty with which it must be assessed ensure that clear answers are not imminent and the debate over the most appropriate path forward in the USA and abroad will continue.

Probiotics

Probiotics promote the establishment and development of a desirable intestinal microbial balance. There is a delicate balance between normal and pathogenic microorganisms. This balance can be upset by poor husbandry conditions, disease, or stressors (eg, transport). Bacteria that produce lactic acid can, in general, be beneficial to the animal; certain yeasts may also be beneficial. Their ability to increase growth and promote health are claimed to be due to one or more of the following factors: preventing colonization of the gut by pathogenic coliforms, altering GI absorption rate, and inhibiting bacterial growth and influencing the balance of bacteria in the gut. The probiotic feed additives consist of selected strains of lactobacilli and streptococci that alter the microbial species present in the GI system to the benefit of the treated animal. Unicellular yeasts are also used. The production benefits are variable, and positive responses are more likely when a stressful management change may result in a change in balance of gut microflora. Thus, they are useful in some cases to minimize GI upsets or to help overcome stress due to weaning or transport. The unicellular yeast fungus may also have beneficial effects on rumen fermentation, thereby improving digestion and feed efficiency. The effect of probiotics in older animals may be reduced because of the well-established, balanced population of microflora that is less sensitive to minor detrimental husbandry challenges.