mary 43, pg. 23. - 28. Vance, Robert D., R. L. Preston, V. R. Cahill and E. W. Klosterman. 1972. Net energy evaluation of cattle-finishing rations containing varying proportions of corn grain and corn silage. J. Anim. Sci. 34:851.

The Present and Future Status of Growth Stimulants in Feedlot Cattle

James E. Fox, *D.V.M.*
Field Research Director
Hess & Clark
Ashland, Ohio 44805

The bovine veterinary practitioner today is called upon to practice a strange type of medicine. All of us upon graduation took some type of oath, or accepted an obligation which in so many words stated that we may choose whom we wish to serve; however, once he has undertaken the care of a patient he must not neglect it. This could be interpreted as being obligated to do everything possible to assist our patients and render services to the best of our ability.

We have thus accepted an obligation to provide services which include sound advice based on scientific facts, for which the practitioner expects to be satisfactorily compensated. I personally feel the veterinarian should become more deeply involved and participate in the selection and supervision of the use of various growth promotants that are available to the industry today.

Since the bovine practitioner is called upon to treat a food producing animal, his drug selection today is not primarily based on drug efficacy or safety in the target animal, but must be selected on the basis of safety to man since man is the eventual consumer of the final product.

The bovine practitioner as a veterinarian may prescribe and administer to his patients whatever drug or other medicines he may legally obtain. This constitutes the practice of veterinary medicine which is subject to the state laws and not under FDA regulations. However, no veterinarian, practicing or employed by a feed manufacturer, or nutritionist, pathologist or any manufacturer may authorize the use of feed with drugs or drug combinations that are not approved for animal feeds. Any individual so doing may be held responsible if drug tissue residues are found in treated animals resulting from the use of such unauthorized medicated feeds.[1]

Thus, in addition to the patient's health and safety, veterinarians must be aware of their possible liability for residues found in food producing animals.

The practitioner, from a practical point of view, is further limited in employing a combination of drugs sinne it has been stated by the Division of Animal Drugs of the FDA that the combination of two or more drugs is only permitted if each drug is shown to contribute to the total effect. With the current efficacy and safety requirements, the bovine veterinary practitioner today must conclude that it is only safe and proper to use drugs and combinations of drugs for which there is an approved NDA. Practitioners in addition have the responsibility of following the label directions for such approved drugs since those label directions must contain dosage recommendations, contra-indications, and proper withdrawal periods. The label must contain adequate information for use under which the drug can be safely used for the purpose for which it is intended, which is based on the submission of sufficient safety and efficacy data as required by FDA.

This constitutes the present criteria for selecting growth stimulants in feedlot cattle, limiting us to the drugs or combination of drugs for which there is an NDA on file. It is generally recognized that growth promotion per se is not a desirable trait unless it is accomplished without loss of feed conversion efficiency. With this concept in mind, and for sake of discussion, we might divide growth stimulants into two categories:

1. Those compounds that are antibiotic or chemotherapeutic by nature and as a result of their presence in the animal's body alter the microflora present and either by the process of reducing undesirable microflora or in some cases altering metabolic processes, have an effect on the final growth rate. Drugs such as chlortetracycline, tetracycline, bacitracin and tylosin fall into this category. In the presence of specific disease conditions these antibiotics are capable of producing some very substantial increases in the rate of gain and improved feed efficiency. However, when they are added to the diet of "normal" cattle they generally are capable of producing slight improvement in daily gains and feed efficiency when compared to nonmedicated controls. Data from several trials[2] indicate a positive response in average daily gains from 2% to 4% and an improvement in feed efficiency of 3% to 4%.

[1]*This is a direct quote of Leon Brunk, Acting Director of Compliances of the Bureau of Veterinary Medicine, FDA.*

[2]*W. Burroughs, 4th Annual Arizona Feeds, Elanco Seminar.*

4. DES

Diethylstilbestrol is a synthetic estrogen available to the cattle industry in two forms, one is a feed additive and the other is in the form of an implant. DES is approved for use in the supplemental portion of feed for both heifers and steers, and as an implant for both heifers and steers. Supplement manufacturers are required to have an approved medicated feed application Form 1800 on file with the FDA prior to manufacturing feed containing the drug.

Approval has been granted for combination use of stilbestrol with tetracycline, chlortetracycline, and bacitracin at specific levels of the antibiotic based on mg/hd/day consumption.

DES premix is currently being marketed by Hess & Clark and also by Dawe's Laboratories.

DES implants are available for use in heifers or steers in the form of pellets to be placed in the ear and currently are not to be used within 120 days of slaughter of the animal. Currently DES implants are being manufactured by three companies - Hess & Clark, Franklin Laboratories, and Vineland Laboratories.

Since there has been some controversy concerning the off and on use of DES, I would like to briefly review the DES situation as it stands today.

DES was discovered in 1938, synthesized in quantity in 1941, and first used in feeding cattle by Iowa scientists in 1953. The mode of action of DES is not clearly understood. However, it is thought by some scientists that this synthetic hormone stimulates an increase in secretory activity of the anterior pituitary which in turn increases the release of an anabolic hormone for adrenal endrogenic activity. In 1954, DES was first marketed after submission and approval of an NDA for the use of DES in feed. In 1955, DES implants were approved by the Food & Drug Administration. In 1958 the Delaney Clause was added to the amendment which prevented the FDA from granting any new approvals or making any changes of any kind in any DES regulations for a period of time. DES had been recognized as a carcinogen for some years, but it was the opinion of a number of scientific experts at that time that DES apparently passed out of the system of the animal in a very short time. As a result, the so-called "DES Clause" was enacted in 1962. Briefly, it stated that it is legal to use a drug such as DES if the drug does not adversely affect the animal for which it is intended, and if no residue of such drug is found by method of examination prescribed or approved by the Secretary by regulation in any edible portions of such animal after slaughter or any food used or derived from the living animal.

Since 1962 carcasses of slaughtered animals were examined for the presence of DES using the approved method which is the mouse uterine assay procedure. Using this test no DES residues in edible tissues were detected under conditions of legal use of DES combined with a minimum 48-hour withdrawal period prior to slaughter. In 1971, metabolism studies indicated that the 48-hour withdrawal period was not adequate and possibly some debilitated or abnormal animal might not be eliminating all of the DES in that period of time. It was also during this period that the USDA, in monitoring carcasses, began using the gas liquid chromatographic method. As a result of this test being a more sensitive test they started detecting small amounts of residues in beef liver. This was reported to the FDA and as a result of these reports the FDA instituted the withdrawal of DES from the market for a period of time. On December 8, 1971, it was recommended that the withdrawal time be increased from two to seven days' period. Then in March 1972, the proposed ban for DES in liquid feeds was issued, and in June 1972 a notice was issued indicating the intent to withdraw dry DES feeds also. At this time the USDA gathered data using radioactive tagged material. Residues of radioactivity were detected in the liver from the single 10 mg oral dose of DES up to and including seven days withdrawal. Time and time again the Commissioner had stated that DES did not constitute a public health problem. On August 4, 1972, the order was published ordering an end to the manufacturing of DES premix. The FDA at this time pointed out that based on field investigations no residues had been found by the USDA of regularly monitoring animals that had been administered DES solely by implants. Studies were instituted with radioactive implants which were manufactured for the USDA by our laboratories. We also conducted an extensive implant study program using conventional testing methods - namely the GLC and mouse uterine assay procedure. Animals in one test were implanted with 30 mg of stilbestrol and then slaughtered at ½, 2, 14, 28, 60, 90 and 120 days after implantation. Samples of the liver and muscle tissues were examined by an independent laboratory. The results showed that no detectable levels of residues were found in muscle tissue of any animal at any time. The only tissue to present a positive reaction to the GLC method was the liver of one of three steers slaughtered two days after implantation. All other animals showed no visible residue to be detectable by the GLC procedure. Similar findings to these were shown by the USDA in additional tests.

On April 27, 1973, the FDA presented the results of studies with radioactive implants and simultaneously issued an order. A radioactive material was identified in the liver at 120 days following implantation of animals with radioactive implants. We demanded a hearing on the basis of the fact that we had not had a chance to examine and comment on the data, about which we had questions and reservations. We were denied the hearing by the FDA; therefore Hess & Clark, along with Vineland Laboratories on behalf of the implants, and Hess & Clark, along with Chemetron Corporation and Dawe's Laboratories, Inc., on behalf of oral DES, filed suits in the U.S. Court of Appeals of the District of Columbia in the Appealate Court against the Food and Drug Administration.

On January 24, 1974, Judge Leventhal filed the

opinion of the court in favor of the petitioners against the Commissioner's orders in both suits. It has been agreed by most legal experts that have read the decision that this decision is of extreme importance not only to the future of DES but may represent a legal opinion that will have considerable bearing on questions concerning other problems of the pharmaceutical and animal production industry.

There are a few points the judge made that I would like to mention.

First, the DES Clause that modifies the Delaney Amendment stated that the residue must be identified by an approved method. In the FDA's case the residue was identified by a method that was considered a laboratory tool.

Second, it has been stated time and time again by the Commissioner that DES does not constitute a public health hazard and the court concluded that the issue should have been resolved at hearings and ruled accordingly. The judge also pointed out that most drugs are unsafe in some degree, and stated that the FDA must consider after the hearings whether DES will be safe in terms of the amount of DES consumed.

He goes on to state that the issues of fact mandate a hearing and the hearing when held may soundly range into interrelated policy issues. From this it can be concluded that the Delaney Clause was not used, that DES was removed from the market due to the opinion of the FDA that it could not be properly regulated. As a result of the January 24, 1974, decision it has been reported[5] that the FDA will do the following:

1. They propose to publish an opportunity for a hearing.
2. They have requested that a 14-day withdrawal period be adopted for feed since they do not feel a seven-day withdrawal period is adequate.
3. They plan to abolish or revoke the official tissue residue method and establish an adequate sensitivity test method.
4. Surveillance will continue by the USDA using the GLC method. If a positive residue is found it will be confirmed in the regulatory laboratory of the Bureau of Foods by mass spectra and no case will be considered positive until it has been confirmed.

In consideration of these proposals it is my opinion that the DiBESTrol-C implants, when properly used as directed, can be safely used by the cattle industry. The decision of whether or not to use oral stilbestrol will require considerable thought. The possibility of drug carry-over to other animal feeds remains a possibility unless complete separate manufacturing and handling facilities are available for feed containing DES and other feed not containing DES. The previous ban on use of DES was based on regulation. We in the pharmaceutical industry can provide expert opinions and suggestions based on scientific data; however, the final use or misuse of DES is in the hands of those directly involved with the cattle industry.

Since January 24, 1974, when DES usage was reinstated, there have been five DES residue violations reported by the USDA.

New Compounds and New Products

There are several anabolic steroids[6] currently being used in some European countries. For example, we have Hoechst Finaplix, which is 300 mg of trienbolene acetate, applied as an implant and also as a delayed release injection under such names as Finajet and Hexabolan. These products have not, and perhaps cannot, pass requirements as required by the FDA. Therefore, they cannot be considered for use in this country. A literature review does not indicate outstanding results from an efficacy standpoint.[7]

There is one area of considerable interest to the ruminant nutritionist and perhaps may be of considerable interest to the total beef industry. This is the consideration of the group of polyether antibiotics that are thought to be capable of assisting and increasing the efficiency of the rumen. Monensin, Lacalocid and Selenomycin are examples of these fermentation products. Eli Lilly scientists have reported in *Animal Science*[8] the compound they are working with changes the proportion of volatile fatty acids produced in the rumen by increasing the proprionic acid while decreasing the acetic and butyric acid. Considerable work is underway to study these compounds and I wish to point out that these new compounds are experimental drugs and must be used under an investigational new animal drug application. There is no clearance of their use in commercially feeding cattle.

Analytical Considerations in the Future

The availability of currently produced growth compounds and the development and approval of any new growth compounds will be most likely dependent upon the ability of technology to develop satisfactory analytical procedures that are sensitive enough to meet the projected requirements. Most scientists feel we should permit the use and development of drugs, including those that are classified as suspect carcinogens, on the basis of the benefit-risk concept, basing the food residue tolerance on biological zero tolerance rather than a chemical zero tolerance.

Benefit in most cases can accurately be defined and sometimes even calculated on an economic basis. However, for every benefit there is a certain amount of risk. The big question then proposed is who will

[5]*DES Regulations. Dr. Kingma, March 1974, IVA Workshop.*

[6]*"Influence growth hormone, anabolic ateroids" Nutr. Health Diseases. Item Symp. Leiden, 1962, 170-84.*

[7]*"The effect of an anabolic thiene steroid on the fattening of non-lactating cows." C. Berangen & Maltarre, Compt. Rend. Soc. Biol., 162.*

[8]*Monensin - (Proprionic Acid) - Abstract in Journal of Animal Science, July 1974, Vol. 39, No. 1, page 250.*

2. The second group of compounds are those anabolic agents that are either hormone or elicit a hormone-like response in the target animal. However, the exact mode on action of these compounds is a difficult problem for the endocrinologist to completely explain. In general metabolic rate is increased slightly then these compounds are administered to the target animal and they are generally capable of causing an increase in total body protein as evidenced by a slightly positive nitrogen balance when they are administered.

I would like to review and briefly bring us up to date on those anabolic agents that are currently marketed. I do not intend to discuss any data with reference to efficacy of these compounds.

Variables, such as age, sex, breed, diet, weight of animal, term of feeding, and so forth, all have a potential of altering efficacy results. Each commercial company has developed and published efficacy data that is readily available to the practitioner. I feel it is part of his professional responsibility to sort out or eliminate the testimonials, select and review the data that has been developed by well designed and controlled experiments. On the basis of this information the practitioner should be able to make a selection of a product for a specific client or feedlot based on their specific needs. Factors such as method of administration, length of time animals will be fed, will have to be taken into consideration. The length of time the animals are to be fed may be the single most important factor affecting your selection of a product, particularly with the long withdrawal restrictions that have been placed on anabolic growth compounds today. These restrictions make it essential that the use of these compounds be programmed throughout the whole feeding period with the projected marketing date being first considered, then determine how the available compounds can be utilized throughout the feeding period.

Anabolic Agents Available to the Cattle Industry Today

1. RALGRO

This implant is available as Ralgro brand of zeranol which is distributed worldwide under the Ralgro label and is available through veterinary distributors in the eastern United States under the name of Ralabol. Between 1957-58, Dr. Staub and Dr. Andrews of Purdue University noted symptoms suggestive of hormonal activity in several herds of swine in Indiana that had been receiving moldy corn. Samples of this mold were submitted to Commercial Solvents Corporation whose microbiologist succeeded in isolating the causative organism, *Gibberella zeae*. Subsequently additional fermentation studies of selected strains of the organism led to the production of the active metabolite in 1961. During the period from 1961 to 1965 many derivatives of the parent compounds were prepared and screened for biological activity. One compound present, zeranol, looked promising in early screening trials. In November, 1969, FDA clearance was granted for use in feedlot steers, with additional clearance in 1970 for suckling and weanling beef calves, growing beef cattle, feedlot heifers, and feedlot lambs. Zeranol is the chemical compound that does not have the molecular structure of newer hormones or their metabolites, yet elicits a hormonal-like response in the target animal, which in turn poses a very difficult problem for the endocrinologist to explain its mode of action. It is thought that zeranol's apparent anabolic response results through its mediating the functions of the pituitary gland. Somatotropin hormone is produced at a higher rate than is produced in a nonimplanted animal.[3] Zeranol pellets are implanted in the ear only and implanted animals are not to be slaughtered within 65 days of implanting.

2. SYNOVEX

Syntex Laboratories offer two products for implanting, one for steers and another for feeder heifers. The purpose of the hormone implant is to supplement or replace the hormone output of the animal's endrocrine system in order to achieve the highest degree of growth efficiency.

Synovex-H for heifers combines the hormones testosterone and estradiol benzoate, while *Synovex-S* for steers combines the hormones progesterone and estradiol benzoate.

Each implant cartridge consists of eight pellets which are deposited on the back side of the ear. This product carries the warning that implants are not to be used within 60 days of slaughter and Synovex-H is not for use in dairy animals.

3. MGA

MGA is melengesterol acetate, a synthetic progestational steroid capable of stimulating rate of gain, improving feed utilization, and suppressing estrus in feedlot heifers. It has no known beneficial effect on steers. The product is manufactured and marketed in the U.S. by TUCO Division of Upjohn Company, and currently is used as a growth promoting feed additive for heifers. MGA has been declared a new drug and is approved for use in the supplement portion of the ration for feedlot heifers with a required 48-hour withdrawal period prior to slaughter. MGA allows the ovarian follicle to develop to maturity but estrus and ovulation are inhibited. The persistence of the mature follicle produces high levels of estrogen which in turn produce a hyperestrogenic state which is believed to be the reason for the improvement in rate of gain of feed efficiency in MGA treated heifers.[4]

MGA is marketed in a premix form and is sold only to feed manufacturers who have an approved medicated feed application Form 1800 on file with the FDA. MGA has not been cleared to be fed in combination with antibiotics.

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[3]*RAL Mode of Action. Endocrinology of Zeranol. August, 1972. Sales Training Manual (2-172), page 48.*

[4]*MGA. JAVMA, 1970, Vol. 157, No. 11, pages 1528-1536.*

determine what risk we should permit. Today there is considerable difference even between the opinion of different scientists. For example, much criticism over the use of DES in cattle has been published and even printed on the front pages of our daily newspapers throughout the United States. Yet, in the *Journal of the American Medical Association*, September 3, 1974, Dr. Thomas Jukes, a well known biochemist and nutritionist for the University of California, declared that by using a risk calculated method based on the known carcinogenicity of DES for humans, he feels that the use of carcasses of beef for food implanted with DES does not constitute a health problem for humans and extrapolates that the risk is "one case of cancer per 2,500 years in the U.S. population."[9]

The method of measurement in the analytical procedure is of primary importance. Adequate, well designed, long term toxicity tests are required to determine biological hazards. Based on this information the sensitivity of the residue method is developed. Today's tissue residue methods as required by regulatory agencies must be (1) validated by the laboratory testing, and both by the FDA and USDA, and (2) the method must be specific for the compound being assayed or a companion confirmatory method for qualitative identification of a specific compound must be substantiated and validated by both FDA and USDA.

There appears to be reluctance of many today to even accept a reasonable risk. We have the supercautious who insist that even one molecule of a suspect carcinogen is dangerous and must be identified whenever it occurs in our environment.

More and more sensitive methods of measuring tissue residues are constantly being required. For example, in 1958 we were required to have a tissue residue for furazolidone sensitive to approximately 1-2 ppm. In 1960 it was raised to .1 ppm, and today they are requiring a 2 ppb and have been attempting to validate a procedure for over two years.

A member of industry submitted to the FDA the gas liquid chromatographic method for assaying tissue residues for DES with a sensitivity of about 2 ppb, but it was not validated; and yet, it is being used today by the USDA to monitor in the field for DES in their surveillance program.

Another classic example of what we can expect can be seen by looking at the projected tolerance for aflatoxin. This substance occurs in the natural diet such as peanuts and currently there is a tolerance submitted somewhere in the range of 20 ppb. However, utilizing the toxicity data that have been developed it will place the projected tolerance in the future in the range of $1\text{-}10^{-15}$ which is at least a million times more sensitive than the present allowed tolerance.

On October 8, 1974, Dr. Kolybe of the Office of Science of the Bureau of Foods in addressing the Animal Disease Section of the Animal Health Institute stated that there will be a statistical and mathematical procedure to determine a safe level of all drugs in the future. If this becomes a regulation FDA has said that any old drugs, as well as any new drugs, will be subjected to the procedure. Unless a major breakthrough in technology occurs we cannot develop suitable analytical procedures to satisfy these projected sensitivity requirements.

In addition to the analytical problems I would like to quote Mr. F. D. Whitlock of Johnson & Johnson, who is also board chairman of the Pharmaceutical Manufacturer's Association, "Statistics indicate that from research and development of a new drug from the first animal testing to FDA approval, the cost is from $10 to $20 million dollars covering a period of seven years. The success rate of any new compound prepared today in the laboratory is placed at one in 7,500."[10]

In summary, I would have to state that in my opinion the possibility of development and introduction of any new anabolic growth compound is not very probable in the foreseeable near future. Compounds that are available to the industry today that today are considered safe and efficacious are all being subjected to very critical review to determine if current accepted sensitivity testing procedures are sufficient to determine if a safe level of the drug or hormone or compound persists in the target animal.

Also, every effort possible should be extended by the practitioner to properly assess the specific needs for a specific situation faced by his client, and then select and recommend the commercial product of his choice and insist on following the manufacturer's recommendations. Deliberate misuse of drugs or growth promoters will not and cannot be tolerated in today's livestock industry.

I can assure you that there are many of us in industry doing everything possible to keep the products we have today and will continue to develop the technological expertise that is required to continue an active research program for new products and methods.

[9]*Dr. Thomas Jukes on DES. JAMA, September 30, 1974, Vol. 229, No. 14, page 1920.*

[10]*Cost of Drugs. Scrip. October 3, 1974, page 5.*