

HISTORY OF HORMONAL MODIFIER USE

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INTRODUCTION

Hormones naturally produced by man and animals result in morphological, behavioral, physiological and biochemical changes that are well known, i.e., men versus women, bulls versus heifers. When used for meat production in many parts of the world, bulls are castrated (steers) to reduce behavioral problems even though this practice reduces growth rate and efficiency of lean meat production. It is not surprising, then, that animal scientists would be interested in modifying the hormonal status of animals to improve efficiency and product composition. Over the past 42 years, results of this research have found widespread application in the production of beef without any safety problems for either humans or cattle. The history of hormonal modifiers can be characterized as a series of developments that have better optimized the dose and combination of compounds for maximum growth, feed efficiency, and carcass quality and minimized cost of production. This paper focuses on the history of the first hormonal modifier to have widespread application and impact in beef production, diethylstilbestrol (DES).

Early Research and Application

Thyroid hormones (e.g., thyroprotein, iodinated casein) were found to increase milk production. Estrogenic activity in several plant foods and feeds was found to be responsible for reproductive problems in livestock. Zondek and Marx (1939), in a single cock, demonstrated that the lipemic response at the onset of egg production could be duplicated by injecting estradiol benzoate. In 1943, Lorenz published a note describing the three-fold increase in the fat content of the breast and leg muscle of cockerels eight weeks after implanting DES subcutaneously, a finding that was applied in the commercial production of broilers from 1947 to 1966.

The first experimental administration of an estrogen, in this case DES, to ruminants for the purpose of growth promotion was done at Purdue University by W.E. Dinusson, a graduate student of F.N. Andrews and W.M. Beeson. They hypothesized that the growth rate in heifers would be affected positively by estrogen, because growth rate of intact heifers is greater than that of spayed heifers. DES was used as the estrogen treatment because DES implants had been formulated for use in poultry by Wick and Fry, Inc., Cumberland, IN. Their first experiment, started on February 9, 1947, utilized twenty-five Hereford heifers that weighed about 225 kg and lasted for 140 days. Five treatments were studied: control, spayed (prior to the start of the study), DES (42 mg implanted in the shoulder region), testosterone (50 mg of testosterone propionate injected initially and 32.5 mg injected at 56 days), and thiouracil (4 gm per animal per day in the feed). The diet consisted mainly of corn and cob meal, soybean meal and mixed clover and timothy hay. The results of this and later studies (Table 1) were first reported November 1948 at the annual meeting of the American Society of Animal Production in Chicago (Dinusson et al., 1948; 1950). A similar second 185 day study was started on December 11, 1947. Three pens of three heifers each, similar to those in the first study, were used on each treatment. The DES implant treatment used was 48 rather than 42 mg, a 50 mg testosterone propionate implant was used rather than oil injections, and a 11 mg per kg body weight oral thyroprotein treatment was used rather than thiouracil. Results of the second trial are shown in Table 2.

The authors drew the following conclusions:

1. DES improved gain and feed conversion
2. DES increased length of leg and back, and width of back
3. DES increased appetite

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Table 1. Effect of hormone treatments on the growth and fattening of heifers.

Item	Control	Spayed	DES	Testosterone	Thiouracil
No. heifers	5	5	5	5	5
ADG, kg.	.94	.87 ^a	1.05 ^a	.95	.97
ADF, kg.					
Concentrate	4.3	4.8	4.7	4.8	4.5
Roughage	2.9	2.9	3.2	3.0	3.0
Feed/gain	7.7	8.9	7.4	8.3	7.8
Dressing percent	58.6	59.7	59.8	59.8	58.9
Carcass grade					
Choice, %	80	80	40	80	60
Good, %	20	20	40	20	40
Commercial, %			20		

^aDifference approached significance (P<0.05) from control.

Table 2. Effect of hormone treatments on the growth and fattening of heifers.

Item	Control	Spayed	DES	Testosterone	Thyroprotein
No. heifers	9	9	9	9	9
ADG, kg.	.78	.70 ^a	.91 ^a	.78	.72
ADF, kg.					
Concentrate	5.4	5.1	5.7	5.3	5.4
Roughage	3.3	3.2	3.3	3.3	3.3
Feed/gain	11.1	11.9	9.9	11.0	12.0
Dressing percent	60.8	59.8	60.6	60.1	60.4
Carcass grade					
Choice, %				11	
Good, %	78	78	56	56	56
Low good, %	11	22	44	22	44
Commercial, %	11			11	

^aDifference was significant (P<0.05) from control.

4. DES carcasses were slightly "hooky" (more mature in appearance).
5. DES caused vulva swelling, extended estrus, produced a nymphomaniac stance, elevated tail heads and pronounced mammary and teat development.

Performance of the spayed heifers was inferior to that of either the control or DES treated heifers as had been expected. The authors suggested that "the rate of gain of these three groups was proportional to the amount of estrogen present".

Results from these two small studies utilizing only 14 animals per treatment predicted quite accurately the response to DES (estrogen) treatment by feedlot cattle. DES generally was expected to increase gain by 15%; these studies showed increases of 12 and 17%. The feed conversion improvement was expected to be about 10%; these studies showed improvements of 4 and 11%. These studies also suggested leanness increased and carcass grade decreased, a general

finding with DES. Despite the absence of any dose titration studies, the implant dosages selected for use in these studies, 42 and 48 mg, were quite close to the dosage (30 to 36 mg) commonly considered optimal later by the feedlot industry.

The side effects of the DES treatment listed in the final conclusion were considered at that time to be very negative and without any immediate apparent solution. These effects as well as a possible reduction in carcass fatness undoubtedly resulted in a considerable delay in the commercial application of this very valuable technology.

The first study using DES in finishing lambs also was conducted at Purdue University by F.N. Andrews in November 1948 (Andrews et al., 1949). The authors concluded that 12 and 24 mg DES implants improved gain and feed conversion, reduced carcass grade and that DES, because of its carcass effects, appeared to have stimulated "true growth" in these lambs. The only side effect reported was the loss of one lamb in

the 12 mg group due to prolapsed rectum. In contrast to the cattle studies, the DES implant doses used in this study were considerably higher than those ultimately used in practice (3 mg).

Oral Administration of DES

The research objective that led to the synthesis of DES was to develop an orally effective estrogen for use in human medicine (Dodds et al., 1938). The first report of the effects of oral administration of DES in ruminants was by W. H. Hale at the 1953 American Society of Animal Production meeting in Chicago, IL (Hale et al., 1953). Hale and his graduate student C. D. Story at Iowa State College fed levels of DES that they felt were comparable in terms of estrogenic activity to the levels of estrogens found in certain legumes purported to increase growth rate. They fed DES at levels of 3.3 to 26.5 mcg per kg of diet. They reported that in two studies these lower levels of DES (3.3 to 6.6 mcg/kg) improved both gain and feed conversion; the higher levels had no effect. A third study found no response to the orally administered DES. The responses that they reported in the first two studies are unexplainable, since the effective oral dosages later were found to be in the range of 660 to 1320 mcg per kg of diet (Hale et al., 1955). Even though these initial experiments on the oral administration of DES did not show a consistent response, they did lead to some very significant studies at Iowa State College.

Hale and Wise Burroughs, a co-author on the Hale papers, discussed the idea of feeding DES to cattle. It was known that DES was not very effective orally in chickens but Hale had seen a research note in a British pharmaceutical journal (source unknown) indicating that DES was rapidly detoxified in chickens but not in cattle (Hale, 1996). Hale and Burroughs conducted a small experiment at the Beech Avenue cattle facility at Iowa State using individually fed cattle that indicated there may be a response to a "high level" of DES (unpublished results).

In the spring and summer of 1953 at the Iowa Southwestern Experimental Farm, Burroughs conducted an experiment that indicated "cattle gains could be increased substantially and that feed costs could be reduced materially by placing 5 mg or more of DES in the daily supplemental feed fed to each steer" (Burroughs et al, 1954a). Subsequent cattle feeding studies were carried out in which he fed levels of DES ranging from 2.75 to 20 mg per head per day to yearling steers fed corn-corn silage or corn-corn cob fattening diets for periods of 46 to 120 d (Burroughs et al., 1954b; Culbertson et al, 1954; Burroughs et al., 1955). Results of three of these studies are shown in Table 3. Burroughs concluded that DES increased gains up to 35% and reduced feed cost up to 20%. He also reported that in these studies no reduction in fatness or meat quality was observed and none of the undesirable side effects previously reported with DES implants were observed. He noted that cattle feeders would not find DES implantation to be practical which he attributed to the following:

1. Potential human health hazard if substantial pellet residues remain in tissues at slaughter.
2. DES implantation appears to adversely influence carcass quality.
3. Implanted animals may exhibit undue restlessness or abnormal sexual behavior.
4. Some animals may exhibit toxicity symptoms (such as uterine and rectal prolapse and difficulty in urination) from DES implantation.

In contrast he suggested that feeding DES was practical because of ease of administration, no undesirable side effects, withdrawal of treatment is possible and feeding allows the accurate administration of a constant dosage of DES. The biological effects of DES in cattle and lambs have been reviewed (Preston, 1975).

Table 3. Effects of DES in the diets of fattening steers^a.

Item	DES/head/d			
	Control	2.5 mg	5.0 mg	10.0 mg
Experiment 1; 46 days:				
ADG, kg.	.96		1.29 ^b	1.13
Feed/gain	11.4		9.3	10.6
Experiment 2; 84 days:				
ADG, kg.	1.13	1.23	1.43 ^b	1.55b
Feed/gain	11.6	10.8	10.0	9.1
Experiment 3; 84 days				
ADG, kg.	1.14		1.43 ^b	
Feed/gain	9.1		8.3	

^aEight steers per treatment.

^bSignificantly different ($P < 0.05$) from control.

Special Iowa State Feeders Day

On February 18, 1954, a special Cattle Feeders Day was held at Iowa State University to announce the discovery of the growth promotion by oral DES in cattle. Previous publicity about a new discovery resulted in a huge and unexpected crowd (over 1000). To accommodate the crowd, the morning and afternoon programs were presented simultaneously. There were insufficient copies of the research report; one of us (RLP) overheard some cattle feeders saying that without a report, they would not be able to show their wives where they had been that day.

Iowa State Patents Oral DES

Purdue University made no attempt to obtain patent protection for the use of DES implants in cattle and sheep (Andrews, 1995). The Purdue administration at that time felt that commercialization of new technology was beyond the academic role of the university (Perry, 1996). However, Iowa State College and Wise Burroughs filed for a U.S. patent on the oral administration of DES to cattle on June 3, 1953 which was granted May 1956. Eighty five percent of the royalties from the patent accrued to the Iowa State College Research Foundation. The patent was based on many of the advantages of feeding DES over implanting suggested in Burroughs' Science publication (Burroughs et al, 1954). At that time, Dr. Jean F. Downing had the responsibility for finding and developing new animal products for the recently formed Agricultural Products Division of Eli Lilly and Co., Inc. The President of Specified Inc. (an agriculture/pharmaceutical company) in Indianapolis, IN, Downing's previous employer, was returning to Indianapolis after attending a Cattle Feeders Day

program at the University of Minnesota. Seated in front of him on the plane were two persons discussing the results of the DES studies at Iowa State. As soon as the plane landed, he called Downing and passed on what he had heard. Downing immediately contacted Lilly patent counsel, called Wise Burroughs and arranged a meeting at Iowa State the following day. Iowa State had made contact earlier with a potential DES manufacturer for development of the product but had received a noncommittal response. Lilly, also a manufacturer of DES, came to the meeting ready to make a commitment to this development project. Lilly also possessed some manufacturing technology that was critical to the safe handling of the drug. As a result of this meeting, and after the President of Iowa State University, James H. Hilton, met confidentially with interested parties in agriculture and approved, Iowa State College granted the exclusive five year license under the patent to Lilly on July 29, 1954 (R.L. Willham, 1996).

Lilly worked with Iowa State College in developing the data needed for the approval of DES by the FDA. The tissue residue data submitted was determined using an immature mouse uterine weight, parallel line bioassay with a sensitivity of 2-3 ppb (Preston et al, 1956). The registration package was submitted to the FDA and DES was approved to be fed to beef cattle at a level of 10 mg per head per day on November 5, 1954. Clearance came only one year after the report of the results from the first DES cattle feeding studies. Within four weeks after FDA approval, the DES premix STILBOSOL was available to feed manufacturers. STILBOSOL was the product that provided the foundation for the development of the animal product business of ELANCO Animal Health.

A quote from A. Marcus (1994, p25) characterizes the university-industry partnership that was at work at that time:

“Indeed, the case of DES seemed to be a model of the application of the partnership idea. A college scientist uncovered a new technique, pharmaceutical scientists produced the drug, feed-manufacturing scientists compounded the material as a premix, federal scientists approved its use, agricultural college scientists publicized it by demonstrating its utility, and farmers made use of it. That type of expert-based interaction had been the model for ‘progress’ since the 1920s. With respect to stilbestrol, little in the mid-1950s seemed to undercut faith in that model.”

Today, this partnership still exists except that pharmaceutical scientists have taken the lead in developing new drugs and combinations.

DES Implant Development

The formulation work on DES implants for use in poultry was done by Bill Wick and Henry Fry who were formulation chemists for Eli Lilly and Co., Inc. This development work was a “moonlight” project carried out in their personal laboratory, a converted garage in Cumberland, IN. They approached George Varnes who was the President of the newly formed Lilly Industrial and Agriculture Products Division to determine if Lilly had an interest in developing DES implants for cattle. Varnes indicated that he was not optimistic about the commercial possibilities for use of growth promoting implants in beef cattle and declined the offer (Means, 1996). Wick and Fry then cooperated with Chas. Pfizer, Inc., Terre Haute, IN in the development of DES implants for use in cattle. Pfizer obtained FDA approval for DES implants for cattle in 1957.

Oral and Implanted DES Used Together

With two commercial product forms available and no specific regulation preventing their simultaneous use, it was inevitable that innovators would try simultaneous use of implant and oral DES in an attempt to produce greater gain and efficiency. Experiments showed a larger total response to DES, particularly in heavier cattle. The results of one of these experiments is shown in the Table 4. This Iowa State study utilized yearling steers that averaged about 345 kg, fed a typical corn, hay and supplement diet for 126 days (Burroughs et al., 1963). Greater responses

were observed with the dual oral and implant DES treatment. Gain was increased 9% by the 10 mg oral treatment and 17% by the dual treatment. There was some suggestion that carcass grade was reduced by the combination treatment. The dual usage of oral and implanted DES was widely used in feedlots even though FDA ruled that dual usage violated regulations but could enforce this only by finding residues in slaughtered cattle by the approved method, the mouse uterine weight assay.

Oral 5 to 20 mg of DES Approved for Cattle

At the time of the original DES clearance for cattle, there were data suggesting that levels of DES higher than 10 mg would produce greater responses. However, it was the opinion of Burroughs and his coworkers (Culbertson et al., 1954) that the 10 mg dosage was close to the optimum and the best compromise at that time. It would seem likely that there was some concern about potential side effects with widespread use in the field. However, the dual usage clearly showed that 10 mg was not the optimal dose and that higher dosages were manageable. Data were developed to support the clearance of feeding a variable dosage of DES (5 to 20 mg per day) and this was approved in 1970. One of the comparisons of the efficacy of 10 and 20 mg is shown in Table 5 (Raun and McAskill, 1965). This study utilized yearling steers averaging about 385 kg fed a complete mixed finishing diet for 127 days. The higher dosage of DES increased rate of gain about 6% and reduced feed required per unit of gain about 4% over the lower dose. Carcass grade appeared to be reduced.

Low Bioassay DES Found to be Less Effective

It was common practice to assay feed and premixes for DES using a chemical assay. It was observed that some feeds and premixes were at or near theoretical DES levels by chemical assay but when assayed biologically, using the mouse uterine weight assay, assay results were in some cases only about 50% of theory (Raun et al, 1970; Hutcheson and Preston, 1971). It was found that these low bioassay DES premixes contained up to 24 percent of the cis- isomer. Purified or enriched preparations of cis- and trans-isomers of DES were prepared, and the efficacy of these two forms of DES were compared in a number of different studies (Raun et al., 1970; Preston et al., 1971). The results of one of the cattle efficacy studies is shown in Table 6. Little if any response was noted with the cis- DES treatment while the expected response was observed with the purified trans- DES.

Table 4. Effect of oral and implanted DES on feedlot performance of yearling steers.

Item	Control	DES	
		10 mg oral/d	10 mg oral/d + 15 mg implant
No. steers	35	34	36
ADG, kg.	1.21	1.32	1.42
ADF, kg.	12.1	12.2	12.2
Feed/gain	10.1	9.2	8.7
Dressing percent	59.2	59.2	59.2
Carcass grade ^a	6.9	7.1	6.8

^a 6 = low choice, 7 = avg. choice.

Table 5. Effect of two levels of DES on feedlot performance of steers.

Item	DES	
	10 mg oral/d	20 mg oral/d
No. steers	63	62
ADG, kg.	1.01	1.07
ADF, kg.	10.4	10.5
Feed/gain	10.25	9.86
Dressing percent	59.0	59.2
Carcass grade ^a	5.50	5.25

^a 6 = low choice, 7 = avg. choice.

Table 6. Effect of cis- and trans- isomers of DES on performance of feedlot steers.

Item	Control	DES	
		Cis- (89%) 10 mg. oral/d	Trans- (100%) 10 mg. oral/d
No. steers	20	20	19
ADG, kg.	1.10	1.11	1.30 ^a
ADF, kg.	7.7	7.6	8.1
Feed/gain	7.04	6.85	6.29

^a Greater than cis- DES (P<0.05).

Early in 1970, a stabilized trans- DES premix was introduced into the market. By this time, there were multiple suppliers of DES operating under a sublicense to the Iowa State/Lilly patent agreement. This premix was promoted by ELANCO as "High Trans Stilbosol" and it had an immediate and dramatic effect on market share. This product designation had to be removed because FDA ruled that an efficacy claim was being made without submission of data; however, the stabilized premix continued to be used as STILBOSOL.

The Rise and Fall Of DES in Cattle Feeding

By the end of 1955, one year after approval of oral DES, it was estimated that six million cattle (~50%) were being fed DES. Eventually, it was estimated that 80 to 95% of the fed cattle received DES in some form. Early on, however, there were industry concerns

and misconceptions about the effects of DES. Physiological (high tail heads and teat development) and behavioral (estrus-like) "observations" were mentioned, mostly because of early experimental observations. Carcass grade and dressing percent reduction were constantly used by packer buyers to reduce the price paid for cattle, something that still plagues the use of implants today (Preston, 1993). Carcasses from cattle given DES were said to be soft and cut "dark". It was even said that water retention was responsible for the growth response to DES, something later proven false using radioactive water (Preston, 1969). These concerns culminated in a special "packer" meeting at Iowa State on a Saturday (4/16/55) where data on the carcass effects were presented, which diminished the rumors somewhat at that time. Corn belt feeders used to feeding small to medium frame cattle on high corn silage diets to a certain final body weight did not realize that higher

energy diets and heavier final weights were required to achieve the same carcass grade, since DES increased mature body weight (Preston, 1978).

The popular and scientific press also misrepresented the safety of beef produced using this new technology. The Police Gazette ran a cover headline "Beef Will Make You Sterile". Nicholas Wade published a "science news" article in Science (1972) where he described DES as "a chemical of bizarre and far-reaching properties, chief of which is that it is a spectacularly dangerous carcinogen" and accused the FDA of political manipulation in an election year. The infinitesimal risk of cancer from eating beef produced using DES was repeatedly made by Dr. Tom Jukes (1976) and others. FDA was under considerable congressional pressure to enforce the Delaney amendment prohibiting the use of any carcinogen if there was a residue in food, the so-called "zero residue" amendment. One person advocated that "Congress needed to enact legislation outlawing all substances that caused cancer in any species, even if no evidence existed that these materials could produce cancer in man" (Marcus, 1994, p40). FDA maintained the position that residues were not found in beef based on the mouse uterine weight assay that was sensitive to 2-3 ppb. During the 1960's, it was found that about 0.5% of the livers, the primary organ of DES excretion, but not the meat of commercial cattle at post-mortem inspection had detectable residues. In the early 1970's, however, this incidence rose to 2-2.5% probably because of dual usage, higher oral doses and, most important, lack of adherence to the required withdrawal periods. FDA prosecuted cattle feeders who did not use DES correctly. USDA studies using ¹⁴C-labeled DES (Aschbacher, 1972) detected presumed residues (<2-3ppb) based on total radioactivity. Since the carcinogenic level of DES in cancer prone laboratory animals was equivocal (Cole et al., 1975), FDA maintained that the carcinogenicity of DES in humans had not been demonstrated. However, after the report (Herbst et al., 1971) of adenocarcinoma in daughters of mothers that had taken massive doses of DES (up to 125 mg daily during the first trimester of pregnancy) that was prescribed (mistakenly as it turned out) for the prevention of threatened miscarriage, FDA had no option except to ban the use of DES in cattle production, even though Herbst later pointed out that this disease was extremely rare even among the DES exposed group which was confirmed by a National Cancer Institute study.

Thus the time-line for the rise and fall of DES use in cattle was as follows:

- 1954 FDA approves oral DES feeding
- 1957 FDA approves DES implants
- 1959-75 USDA isotope studies show DES residues <2-3ppb
- 1972 FDA bans oral DES; 120 day withdrawal on DES implants
- 1973 FDA bans DES implants
- 1973 FDA prosecutes cattle feeders with "DES contaminated" cattle
- 1974 U.S. Court of Appeals overturns ban; FDA failed to hold proper hearings
- 1977 FDA holds DES hearings
- 1979 FDA bans all use of DES in cattle production

Epilogue

The use of DES in cattle and sheep became the victim of zealous attempts to protect the public from all risk. Needless to say, the use of DES in cattle and sheep was not treated objectively by politicians and the press who put unbelievable pressure on the FDA. As Marcus said (1994, p6), "no one could prove that DES beef had harmed a single member of the populace. Conversely, no one could prove that it had not". It is our opinion that if DES had not been banned, it would still rank as one of the most effective cattle growth promotants and that human safety would have never been compromised with proper use. Feeding DES offered dosage and withdrawal control not available in implant products. However, the removal of DES from the marketplace allowed for the development and use of a number of alternative products, listed in the following chronology, that came to the market only after significant expenditures of research time and money, and regulatory agency effort, all of which could have been directed toward the discovery, development and approval of new technology for the cattle industry. It is ironic that we still do not have a clear explanation for the mode of action of estrogen growth promotants in cattle and sheep.

Chronology of Cattle Anabolic Agents in the U.S.

- 1954 Oral DES approved for cattle
- 1956 Estradiol benzoate/progesterone implants approved for steers
- 1957 DES implants approved for cattle
- 1958 Estradiol benzoate/testosterone propionate implants approved for heifers
- 1968 Oral MGA approved for heifers

- 1969 Zeranol implants (36 mg) approved for cattle
- 1982 Silastic estradiol implant approved for cattle
- 1984 Estradiol benzoate/progesterone implants approved for calves
- 1987 Trenbolone acetate (TBA) implants approved for cattle
- 1991 Estradiol/TBA implants approved for steers
- 1993 BST approved for lactating dairy cows
- 1994 Estradiol/TBA implants approved for heifers
- 1995 72 mg Zeranol implants approved for cattle
- 1996 Estradiol/TBA implants approved for stocker cattle

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