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		

[a]Difference 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	

[a]Difference 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	

[a]Eight steers per treatment.
[B]Significantly 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.