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Illinois Agricultural Experiment station, Urbana

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P. J. Dziuk
Illinois Agricultural Experiment Station, Urbana

Control of the estrous cycle is essential to precise research in gamete and zygote physiology and could be useful in animal husbandry. The conception rate in sheep during the breeding season following treatments to control ovulation has varied from about normal (Dauzier, 4; Robinson, 20; Evans et al., 9; Lamond and Bindon, 17; Brunner et al., 3; Hinds et al., 13), to distressingly low levels in other cases (Braden et al., 2; Davies, 5; Lamond, 16). Treatments during the anestrous season have given a variable response but usually only 30 to 50 percent of ewes lamb (Gordon, 13; 14).

In swine, treatment by either injected progesterone or orally administered progestogens has usually caused cystic follicles, only partial control over ovulation, and low fertility (Baker et al., 1; Nellor, 18; Nellor et al., 19; First et al., 10; Gerrits et al., 12) found no adverse effects on fertility from injected progesterone. High levels of progestogens followed by an ovulating gonadotrophin controlled ovulation time but incidence of heat and fertility was low (Dziuk and Baker, 6).

The following report is a compilation of published and unpublished research on sheep and swine to control the estrous cycle.

Materials and Methods

Sheep: Seven hundred aged ewes with a predominance of Merino breeding were treated in groups of 5 or 10. They were killed by electrocution at a prescribed time and examined for follicular growth, ovulation points, and fertile eggs or embryos. An additional 600 ewes were treated in groups of 10 to 40 and allowed to lamb. These ewes were of a variety of backgrounds. Most were mated to a specific ram and his fertility was determined. Six-methyl-17-acetoxyprogesterone (MAP) was administered for 14 days as part of the daily diet, usually at 50 to 75 mg. daily per ewe. Injections of pregnant mare's serum gonadotrophin (PMS) were made subcutaneously (SQ) just behind a front leg at levels of 500 IU, per ewe. Human chorionic gonadotrophin (HCG) was given intramuscularly (IM) at either 250 IU, or 500 IU, per ewe. Estradiol cyclopentylpropionate (ECP) was given intravenously (IV) as an oily solution at 1 or 2 mg. per ewe.

Swine: Two hundred fifty-eight gilts and sows in 14 different groups were fed 120 mg. MAP per day per female for 18 days. Each group also had untreated controls of the same background mated to the same boars as a treated group. These groups were at several different farms, under different management systems, at different seasons, and were composed of several different breeds and ages of females. Gilts not pregnant were killed and the appearance of ovaries and uteri noted. Forty-eight prepuberal gilts about six months of age were treated with 500 mg. of MAP for 9 days and observed for heat.

One hundred eighty prepuberal gilts, 5 to 5½ months old, were treated to induce follicle growth and ovulation with mixtures of 125 IU, of PMS plus 125 IU, of HCG or 250 IU, of PMS plus 125 IU, of HCG, as shown in table 5, or by orally administered ethynil estradiol (EE). They were all checked daily for heat. About half were killed and examined 6 to 8 days after treatment. EE was given orally to each of 10 cycling gilts for 5 days at a level of 16 mg. daily. Seventeen other cycling gilts received 20 mg. EE daily for 15 days. Prior heat dates were known and subsequent ones noted.

Sixty-eight gilts with at least one previous heat were injected with 250 or 500 IU, of HCG about 24 hours before expected estrus as judged by previous heat date, behavior, and appearance of the vulva. These gilts were killed or laparotomized 2-14 hours after ovulation and examined for ovulation points and the eggs were individually examined as fresh, whole mounts, and in most cases also as fixed and stained preparations.

Results and Discussion

Sheep: Of 288 ewes treated during the breeding season, 275 (95%) showed heat over the 24 hour period beginning 48 hours after last MAP and 162 (59%) lambed to this service. The conception rates among treatment groups were not significantly different. The conception rates among rams ranged from zero to 85% and within treatment groups there were differences due to rams in nearly every case. This points out the importance of recognizing differences among rams when trying to evaluate fertility after a treatment.

While the time of heat was well correlated with the last feeding of progestogen, the...
The daily administration of 200 mg. of MAP to 20 ewes inhibited heat and ovulation during administration and for at least 5 days after the last feeding. About half the ewes did not show heat for at least 20 days. An examination of the ovaries of representative, treated ewes revealed several different conditions. Some had no follicular development and no corpora lutea, some had follicles 5 to 8 mm. in diameter and no corpora lutea, while others had ovulated but had not shown heat. It is possible that the progestogens were no longer present in the system but that the high levels after withdrawal caused a delayed recovery.

The administration of PMS near the end of the breeding season did not increase significantly the number of lambs born per pregnant ewe over non-PMS treated ewes. In those experiments in which direct comparisons are possible, there were no statistically significant differences due to time of PMS administration relative to the last MAP feeding (table 2).

Incorporation of HCG with PMS as a follicle stimulator resulted in 78% of ewes showing heat as opposed to 95% of similar ewes not given HCG. Only 37% of ewes receiving HCG with PMS lambed as opposed to 59% of similar ewes not given HCG. Other ewes treated in a similar manner but examined for ovulations had ovulated prematurely as a result of the injection intended to be a follicle stimulating injection. In one experiment neither HCG nor ECP caused high fertility, even though HCG is known to cause ovulation in all ewes similarly treated and ECP causes heat in all ewes (table 3). It may be possible to induce both heat and ovulation by combining the HCG-ECP treatments and thereby increasing fertility.

Swine: Daily administration of 120 mg. of MAP per gilt for 18 days did inhibit heat and ovulation and after withdrawal, heat was synchronized in a certain portion of gilts but conception rate and litter size were significantly smaller than for untreated controls (table 4). Two hundred other gilts not shown in the table were examined after treatment and mating, if it occurred. Sixty, of 200 gilts, had one or more unruptured follicles 15 mm. or larger. Twenty-two of these 60 had only large follicles, 23 had large follicles plus corpora lutea, and 15 of these were pregnant and also had large follicles and corpora lutea of normal appearance. During the course of these experiments, other gilts that were late and ovulated very few follicles or failed to ovulate, while some ovulated and did not show heat. There was a great deal of variability in response not readily explained on the basis of obvious differences within and between groups.

Administration of 500 mg. of MAP per gilt daily for 9 days inhibited heat and ovulation. Injection of 500 I.U. of HCG 5 or 6 days after last MAP feeding, caused ovulation in 94% of gilts but heat occurred in only 4% of animals after withdrawal (Dziuk and Baker, 6). Fertility was low, due at least in part to poor sperm transport to the site of fertilization. Fifty or 100 mg. of diethylstilbestrol (DES) injected about 24 hours before insemination did raise the level of fertility of eggs but interfered with implantation (Dziuk and Polge, 7). Forty-eight gilts were treated with 500 mg. MAP daily for 9 days at about 6 months of age but before their first heat. Only 4 showed heat during the following 21 days and very few had shown heat even 60 days later. This indicates a persisting effect on the onset of puberty due to even a short treatment with high levels of MAP.

The oral administration of 16 mg. of EE daily for 5 days to 10 cycling gilts inhibited heat for an additional 12 days presumably by maintaining the existing corpora lutea as shown by Gardner et al., (11). Seventeen cycling gilts were given 20 mg. EE daily for 15 days. None showed heat for the next 40 days. Seven were killed and all had corpora lutea that appeared normal; at 50 days after treatment 5 more were killed and at 80 days the remaining 5 were killed. None showed heat prior to killing and all had corpora lutea that appeared normal; at 50 days after treatment 5 more were killed and at 80 days the remaining 5 were killed. None showed heat prior to killing and all had corpora lutea. The uteri were enlarged and vascular and had the appearance of a pregnant uterus except that no fetuses were present. If gilts were started on EE treatment during days 15 to 19 of the cycle they came into heat in the next few days as expected, but if treatment started on days 1 to 13 of the cycle they did not show heat.

Twenty prepuberal gilts, 5 to 6 months of age, were given 20 mg. of EE orally for 5 days. Fifteen were in heat on the 4th, 5th, or 6th day after first treatment. Ten showing heat were examined 8 days after the last EE. Eight had ovulated but had an average number of corpora lutea of only 4 per gilt. Each gilt also had an average of 9 follicles, 4 to 5 mm. in diameter. Only one of the remaining 10 gilts showed heat during the next 60 days, indicating a persisting effect.

A single intramuscular injection of either 250 or 500 I.U. of HCG given to 68 gilts in late proestrus caused ovulation in 67 of these and eggs were recovered after ovulation and used for other studies. The mean number of corpora lutea of 4.08.
lutae per gilt was 14.7, indicating that the injection did ovulate the number of follicles that might be expected at a normal ovulation. There was no indication that fertility was affected.

A single subcutaneous injection of a mixture of PMS and HCG given to 180 prepuberal gilts, 5½ to 6 months of age, caused heat 4, 5, or 6 days later in 81 (45%) (table 5). Seventy-two percent of those examined had ovulated. Apparently the single injection of gonadotrophin is a sufficient stimulus to cause follicle growth, heat, and ovulation. Only 8% of animals had a second heat about 21 days later. This treatment then does not initiate regular cycles.

**Summary**

**Sheep:** Withdrawal of daily oral administration of 50-75 mg. of MAP to ewes during the breeding season caused synchronous heat in 95% of animals. Fifty-nine percent produced lambs to this heat. The differences among rams in conception rate were greater than differences among usual treatments. Ovulation time was not well correlated with onset of heat in all animals. Treatment of anestrous ewes with MAP alone or with MAP and PMS caused heat in 67% of 190 ewes and 27% of 190 ewes produced lambs to the first service.

High levels (4X) of MAP for 7 days delayed heat and ovulation for at least 5 more days after last MAP treatment. PMS given near the last MAP feeding did not increase the number of lambs born and had no adverse effect. It appears that PMS is equally effective when administered either zero, 24, or 48 hours before the last MAP feeding. HCG caused ovulation to occur and ECP induced heat but neither increased the conception rate.

**Swine:** The daily administration of 120 mg. of MAP for 18 days inhibited heat but upon withdrawal the conception rate and litter size were below the level of untreated controls. Follicles developed to large size but failed to ovulate in 30% of gilts. Increasing the daily dose of MAP to 500 mg. and shortening the treatment period to 9 days, followed by HCG, permitted precise control over ovulation time but incidence of heat and fertility was low. DES given before insemination increased the fertility level of eggs but adversely affected embryo survival. HCG caused ovulation when given to proestrous gilts.

EE given orally to normally cycling gilts for 15 days inhibited heat for 40 days by presumably maintaining the corpora lutea when started on the 1st through the 13th day of the estrous cycle. When started on the 15th through the 19th day of the estrous cycle, the next heat occurred as expected but the second heat was delayed for at least 40 days. Prepuberal gilts given EE for 5 days showed heat and ovulated near the fifth day of treatment. A single subcutaneous injection of 500 I.U. of a PMS-HCG mixture to prepuberal gilts caused heat and ovulation about 5 days later. Neither treatment of prepuberal gilts caused onset of normally recurring estrous cycles.

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(11) Gardner, M. L., First, N. L. and Casida, L. E.

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(13) Gordon, I.

(14) Gordon, I.

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(16) Lamond, D. R.

(17) Lamond, D. R. and Bindon, B. M.

(18) Nellor, J. E.

(19) Nellor, J. E., Ahrenhold, J. E., First, N. L. and Hoefer, J. A.

(20) Robinson, T. J.
Table 1.--Heat and ovulation relative to last MAP in ewes\textsuperscript{a}

<table>
<thead>
<tr>
<th>Last MAP to killing</th>
<th>Total ewes</th>
<th>Ewes in heat</th>
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<td>9</td>
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\textsuperscript{a} Modified from Dziuk et al., 1964.

Table 2.--Effect of PMS and time of administration on heat and fertility in ewes

<table>
<thead>
<tr>
<th>Flock</th>
<th>Treatment</th>
<th>Time of PMS to last MAP</th>
<th>Total ewes</th>
<th>Ewes in heat</th>
<th>Lambed to first heat</th>
<th>Lambing rate\textsuperscript{a}</th>
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<td>19</td>
<td>9</td>
<td>1.33</td>
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\textsuperscript{a} Lambs born per ewe lambing.
\textsuperscript{b} Anestrous ewes.

No statistically significant differences between treatments in the proportion of ewes showing heat, the conception rate, nor the lambing rate.
Table 3.—Effect of HCG and ECP on heat and fertility in ewes

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<tr>
<th>Flock</th>
<th>Treatment</th>
<th>Dose</th>
<th>Route</th>
<th>Time relative to last MAP</th>
<th>Total to last MAP</th>
<th>Ewes in heat</th>
<th>Lambed to first heat</th>
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<sup>a</sup> Subcutaneously.  
<sup>b</sup> Intramuscularly.  
<sup>c</sup> Mg. Intravenously.  
<sup>d</sup> Intravenously.  
<sup>e</sup> 250 IU PMS plus 250 IU HCG.

No statistically significant differences between flocks or treatments.
### Table 4: Fertility in swine after treatment with MAP

<table>
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<tr>
<th>Herd</th>
<th>Treatment</th>
<th>Total Gilts</th>
<th>Gilts in heat&lt;sup&gt;a&lt;/sup&gt;</th>
<th>To first mating</th>
<th>To second cycle</th>
<th>Total</th>
<th>Mean pigs born per pregnant sow</th>
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<td>20</td>
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<td></td>
<td></td>
<td>71%**</td>
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<td>187</td>
<td>78%</td>
<td></td>
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</tbody>
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<sup>a</sup> Gilts in heat days 4-8 after last MAP.
<sup>b</sup> Not permitted to mate.

** MAP inferior to None (P< 0.01).
Table 5.--Response of prepuberal gilts to a single subcutaneous injection of gonadotrophin

<table>
<thead>
<tr>
<th>Dose IU³</th>
<th>Total gilts no.</th>
<th>Gilts in heat no.</th>
<th>Ovulating %</th>
<th>Corpora lutea per gilt ovulating no.</th>
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<tr>
<td>250</td>
<td>35</td>
<td>18</td>
<td>67</td>
<td>14</td>
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<td>250</td>
<td>22</td>
<td>9</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>500</td>
<td>83</td>
<td>36</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>500</td>
<td>40</td>
<td>18</td>
<td>75</td>
<td>17</td>
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</tbody>
</table>

³ Equal proportions of PMS and HCG.

* Gilts in heat days 4-6 after injection.
DISCUSSION

Dr. CASIDA: There is in the audience a potential speaker who was approached earlier about presenting a paper. For some reason he was not inclined to prepare a paper but he did indicate his willingness to comment upon his work and in fact give us a look at it. I am going to call upon Dr. Wiltbank to tell of some of the work he has been doing at Fort Robinson, Jim.

DR. WILTBANK: I want to mention briefly two experiments that we have conducted at Fort Robinson. The first of these we conducted to determine length of heat, time of ovulation, ova transport, fertilization rate, and embryonic loss in a group of cycling heifers and a group of synchronized heifers.

We had approximately 50 heifers in each one of these groups. We synchronized the heifers by feeding them 500 mg. of a product from E. H. Squibb and Company called proxone, an acetophenone derivative of 16, 17 dihydroprogesterone. This was individually-fed daily. We checked heat on these heifers at four-hour intervals over the length of the experimental period. Ovulation was determined by rectal examination. We examined the heifers at the beginning of heat, twelve hours after the start of heat when they were bred, and then, as soon as estrus ended, we examined them every four hours until ovulation occurred. Forty-eight hours after ovulation, egg recoveries were attempted in half the heifers in each group. We did this by a high lumbar laparotomy. We removed the oviduct and approximately two inches of the uterine horn. Then we cut the oviduct into thirds and flushed each third separately and examined for the presence of the ova.

Now let me show briefly some of the data we have. This is the length of heat in the two groups of animals. (Slides were here projected onto a screen.) The average in the cycling heifers was 22 hours and in the synchronized heifers 16-1/2 hours. Most of the cycling heifers stayed in heat longer than 20 hours. Our synchronization process definitely affected the length of heat with this particular compound.

When we timed ovulation from the start of heat, little or no effect was noted on the time that the heifers ovulated. The average length in both groups was 33 hours. There was an effect on the length of time from the end of heat until ovulation. This averaged 11 hours for cycling animals and approximately 17 hours in the synchronized animals.

Now, let me show the egg recovery and the fertilization rate on these two groups of animals. The percentage of eggs recovered was low, 64 percent in each group. We feel that this is because of the frequent palpations near the time of ovulation. We had some other heifers that we were recovering eggs from at approximately the same time as these in which our egg recovery was 85 percent. The numbers of eggs with a broken zona pellucida were one in the cycling and three in synchronized animals. The number of normal eggs recovered was 13 in each group. Preparation of normal eggs fertilized was 12 of 13 in the cycling, and 9 of the 13 in the synchronized heifers. Percent of fertilization in recovered eggs was 86 percent in the cycling heifers and 56 percent in the synchronized group. There was a difference in fertilization in favor of the cycling animals and perhaps a few more eggs that had a broken zona pellucida in the synchronized animals.

Now, as far as ova transport is concerned, the location of the eggs is shown here. (Another slide was projected on a screen.) The total eggs recovered was 14 in the cycling and 16 in the synchronized. Eggs in section 1--this is a section up closest to the infundibulum—one in the cycling and one in the synchronized. Eggs in section 2: 11 eggs in each case. Eggs in section 3: 2 in the cycling and 4 in the synchronized. These data show very little effect on rate of ova transport.

Now, there is a bad thing about these data. The fertilization rate results are not confirmed by the 34 day pregnancy data obtained from the other half of the heifers. We had 26 percent of the cycling heifers that we found pregnant at 34 days versus 54 percent in the synchronized heifers. So what we found in fertilization was just the reverse of what we found in pregnancy diagnosis.

We are repeating this particular project at the present time and we are getting our ovulation data separate from our fertilization data, running two cycles on another group of heifers. The data have not been completed yet. Now there is one other thing that I would like to mention while I am up here. I differ with Dr. Casida and Dr. Zimbelman on the fact there is not a method for destruction of the corpus luteum. We have data at Fort Robinson in connection with the cow that shows the injection of estrogen, 5 mg. of estradiol valerate will definitely cause regression of the corpus luteum. We can get it in 90 percent of the cases. So I do believe there is a method for destruction of the corpus luteum.

Now there is a thing that happens when you inject estrogen near the end of the cycle, the 16th or 17th day of the cycle, you can cause the animal to go cystic 80 to 90 percent of the time. So you have this after-effect of these injections near the end of the cycle. But in mid-cycle and during the early part of the cycle, you can destroy the corpus luteum and the animal will come back into heat earlier than you would expect it to.

There is another thing I wanted to mention this morning on synchronization of heat that I
think it is important. Dr. Zimbelman mentioned that we have a hyperestrogenic effect when we feed MAP. We have evidence at Fort Robinson that when we inject progesterone plus estrogen, we can decrease our dose of progesterone tremendously and still get synchronization. We have gone down to as low as 10mg. of progesterone daily when we add 160 micrograms of estrogen and we got very good synchronization. In fact, we can induce synchronization with as short an injection period as 10-12 days, which would indicate that perhaps we are getting some regression of the corpus luteum and then be able to synchronize these animals.

DR. CASIDA: Thank you, Dr. Wiltbank.

While you are getting your questions formulated, I would like to raise a question or two with my colleagues.

Dr. Dziuk, did you intimate that there may be a different set of ram differences in fertility when they are used on synchronized ewes that when they are used on normal cycling ewes? In other words, ram A and B may differ from each other when used on synchronized ewes, but the spread between them will differ when they are used on normal ewes.

DR. DZIUK: Yes, this is a part of the problem because a ram may mate one ewe or two ewes in heat today, several times, and finally settle them, whereas, if he has an allotment of eight ewes and all of them are in heat, he mates at least once or twice with each ewe so we know that mating has taken place. This may not be the same as turning them loose with one or two in one day. I am going to hedge on the question because I think it may be related to the capacity of the ram that we cannot measure when he is turned loose, or just by single semen evaluation of any kind. He may appear to be perfectly fertile and not be fertile under the conditions, where eight or ten are in heat in one day.

DR. CASIDA: Thank you, Dr. Dziuk. I raised the question on the possibility of bringing out differences between ram sperm when they are subjected to the environment of post-synchronization as compared to cycling. Now, your difference between return ewes at the second heat and the first heat is actually following the synchronization compared to no synchronization, is that not right?

DR. DZIUK: Yes. That is true in most cases. We thought the second heat after synchronization was less fertile than the first, so we grouped the animals so their first heat coincided exactly in terms of the day of the calendar as the second heat of others, and we still got all these differences, and we didn't get any differences between the treatments. The first cycle seemed to be as fertile as the second one when we took the ram differences and the season differences.

DR. CASIDA: I would like to raise one question with Dr. Wiltbank. He has referred to the regression of corpora lutea when he has used estrogen. I would like to ask: Is this the regression of a fully formed corpus, or is it the prevention of the formation of the young corpus?

DR. WILTBANK: It is a regression of the fully formed corpus luteum because we have injected heifers at the 7th and 10th day and the corpus luteum regresses. And if you inject heifers the 3rd or 4th day of the cycle, the corpus luteum will go ahead and you can palpate it by rectal examination to be 18 to 20mm., and then it will start regressing. So it is not prevention of formation, but regression.

DR. CASIDA: I raised that question because there is evidence of differences in usage of the term "luteinizing," or "luteotropic," or "luteotropic" action. We may need to distinguish between those things which bring about the formation of a normal corpus from those things which maintain the structure and function of a normal corpus.

I would like to raise the question with Dr. Zimbelman from this morning's discussion with regard to this post-partum cows he is treating with MAP and in which there appears to be an acceleration of ovarian activity in terms of the first post-treatment ovulation. Is this actually an acceleration of activity or is it the prevention of what may have been quiet ovulations in untreated animals so that corpora lutea did not have to be "cleared out" of the ovary before they came back into estrus after treatment?

DR. ZIMBELMAN: I am not sure that I have the question completely straight, but let me start here. Our initial hope was that we would have cows which would not ovulate until 45 or 50 days post-partum, in which case we would have had a distinct shortening of the interval. As you can see, our intervals to first post-partum ovulation were 37 days or less, and therefore we were not able to really shorten it as much as we had hoped. I think that all we can say is that we synchronized these cows by starting them on treatment prior to the time that they began normal estrual cycles, but we cannot say that we really initiated them before because, as you know, some of our controls did ovulate during treatment, whereas the treated animals did not. So, in a sense, there were many animals which we only delayed as you would an already-cycling animal until the end of treatment, but, if this had been the only thing, I think you would expect an average interval from last feeding for control animals of about 11 days, based on chance alone.

If you treated cows that were coming in on each of 21 days on chance alone, you would have the average interval of untreated animals of 10-1/2 days, and over average was about 8 days, so this would indicate that perhaps some animals were being speeded up by a few days. Is that reasoning clear?

DR. CASIDA: Thank you, Bob. I raised this question in part because I agree with you.
thoroughly on the difficulty of palpating the post-partum ovary in a beef cow, and the frequent inaccuracy or inability to pick up corpora lutea at that stage, so it would seem to me that this quiet ovulation might have been a factor in this situation.

DR. ZIMBELMAN: I would like to ask Dr. Wiltbank how much variation there is in the interval from the injection of estradiol valerate to the regression of corpora lutea in animals of different stages of this cycle?

DR. WILTBANK: The corpora lutea will regress anywhere from 4 to about 10 days after the injection of the estradiol valerate, so that it is not a very consistent time.

DR. CLARENCE HULET, USDA, DuBois, Idaho: This is not a question, but I think that I have an answer to Dr. Dziuk's question.

We designed a synchronization experiment in which we fed MAP to ewes in such a way that both those which had been synchronized subsequently would come in heat at the same time; the first group having their post-treatment estrus simultaneously with another group having their second post-treatment estrus. We still got this difference in fertility. In other words, of those which had their first post-treatment estrus but which were mated at the same time as those which were simultaneously having their second post-treatment estrus, 60 percent lambed to that mating, whereas 80 percent of those which had their second post-treatment estrus lambed to simultaneous matings.

DR. CASIDA: Thank you, Dr. Hulet.

Now there has been a question handed in which I will ask Dr. Dziuk to answer. Why is ECP fatal interarterially and not intravenously?

DR. DZIUUK: I presume that the artery is carrying this oily solution directly to the brain and, probably crudely stated, "clogging" up the works. And intravenously it apparently makes a circle around the body and, if it does do damage, it does it in such scattered areas that it does not do any real harm. A suggestion here that it could be due to hemorrhage is not very likely, because intrarterial injection of these oily solutions has an immediate effect, in something like five seconds.

DR. DHINDSA from Illinois: Is death due to the ECP or the injection of the oil into the artery?

DR. DZIUUK: The only injections we made were ECP and oil, so that I cannot say that I have separated them out, but my guess is that it is the oil itself.

DR. CASIDA: I would like to ask Dr. Hansel to come forward and take care of a question growing out of this morning's discussion.

DR. HANSEL: Thank you, Dr. Casida. This is asked by Dr. Dhinda, and I am not sure that I can really answer this. It is:

"What is your definition of cystic follicles insofar as size, color, etc., in pigs and in cattle?"

This is not an easy question to answer off-hand as most of you know. There are certain histological abnormalities that accompany cysts, such as luteinization of theca interna. I doubt that there is any arbitrary size that one can place on this, say beyond this size it is a cyst, and below this it is not. It is something I would be glad to discuss with you. Some of the more detailed observations one can see histologically, but I do not want to get into a long discussion of them now.

DR. CASIDA: I was thinking that Cornell University had given the classical definition of a cyst, that it had to be a structure in the cow that was more than 25mm. in diameter.

DR. SORENSON, Texas A. & M: I would like to make on comment first and then ask a question.

The comment concerned first and second estrus breeding. We put a group of Santa Gertudis heifers on an experiment in which we bred 52 of these heifers at the first synchronized estrus, skipping first estrus on an additional 52 and breeding at second estrus. And then we had a third group of 52 heifers that were controls.

The first estrus group, that is, those breed at their first estrus, had 25 percent conception. The second estrus group, the one that we skipped the first estrus, had 34.6 percent conception.

If you want to make comparisons between the second breedings, the group that we bred the first estrus and then followed up with a second breeding also, we got 40 percent conception. So this sort of "blew" out idea that if we skipped this first estrus, we would get most of them at the second estrus. We actually got more in the ones that we bred at first estrus, picking up at the second estrus, than we did where we skipped the first estrus.

In our control animals, at first estrus we got 54 percent conception, followed with a 17 percent conception on second estrus. So I am still concerned about our second estrus. I am not sure that we can skip this first one and expect to pick up as many as we thought on second estrus.

Now I have a question.

One of the side-effects that we have noticed in cattle breeding, following our synchronization of estrus, has been the copious mucus secretion. This was mentioned just briefly this morning, but no comment was made on it. We have found, especially in some of our crossbred cattle, that as much as 500 cc of mucus may be expelled from the vagina at the time of breeding. This is when the animals are in estrus two to five days following the last feeding. This has been both with MAP and with CAP.

Our last trial with MAP was one I think that was most critical. We had a group of Brangus cows. These cows had calves by their side and were fed for an 18-day period, 150 mg. per day level. There was very much mucus
present at the time of breeding, and I would like for some comment here to be made on what effect this may have upon our conception rates.

DR. CASIDA: I think I shall ask Dr. Zimbelman if he has any further comment on this question.

DR. ZIMBELMAN: If you will recall, the animal which I showed you this morning in Trial A that had received 100 and 500 mg. of MAP as a single injection and slaughtered at 126 days after injection, the animals on 500 mg. had a highly significant increase in uterine weight.

On gross observation, I would say this was primarily due to an accumulation of mucus, primarily cervical mucus. Some of the uterine horns did contain mucus, but this was very tenacious.

It wasn't at all fluid like as I think Dr. Dutt described the accumulation which he had noted in ewes.

This was not present in the 100-mg. MAP group. But most of these animals had returned to ovulation and therefore had perhaps experienced an opportunity to pass this mucus.

Based on these data alone, we cannot differentiate between the possibility of it not being produced by 100-mg. dose, in contrast to the possibility that the mucus had a chance to pass by the animal having experienced one estrous cycle.

Based on some other observations, I think probably the latter choice is correct and that is, if we use oral administration, we have not observed much increase in mucus, particularly on short-term treatments as Dr. Sorenson is referring to. I have no explanation, no prior observations that are similar to those.

We do have some longer-term treatments with oral progestogens in which we have a slight accumulation of mucus, but if the animals were killed at 8 days after treatment, the uterine weights were actually reduced, indicating that the mucus was contributing primarily to the uterine weight increase.

DR. CASIDA: Thank you, Dr. Wiltbank. I shall ask Dr. Wiltbank to make a comment in this regard.

DR. WILTBANK: We have not seen an increase in mucus in our synchronized animals. We have done most of our work with the product of Squibb, although we have done some with MAP, and we never noticed the increase in mucus there.

DR. CASIDA: Thank you, Dr. Wiltbank. Are there other comments to this question or this point of Dr. Sorenson's?

DR. WAGNER of Eli Lilly: In reference to the mucus situation, I would not want to leave anyone with the impression that MAP is the only progestogen that causes copious mucus flow.

We have seen this almost 100 percent of the time, not in 100 percent of the animals. In 100 percent of the studies we have conducted, both at Greenfield and other places, we saw this mucus in 50 to 60 percent of the animals. It seems to be more prevalent in those animals which are started on treatment toward the middle of the cycle where they have an extended follicular phase throughout the gestational period.

I think possibly Dr. Zimbelman's comment that 10 mg. is a little high in cattle is correct. Upon Dr. Hansel's suggestion, we reduced this 10 mg. dosage of CAP the latter half of the feeding period, nine days, to 5 mg. and the mucus was less than normal at the heat period. We had I think 28 animals. Twenty-six showed heat within a 36-hour period and actually, upon insemination, only two or three showed any mucus discharge at all. In all respects, vulvar swelling, mucus discharge, the intensity of the heat, appeared to be more normal, with the exception of mucus being a little less than normal.

This is very recent and we have only had a chance to look at it once. I think it does deserve comment because mucus has been brought up in the discussion as an abnormal function in this first synchronized heat following progestin treatment.

DR. CASIDA: Thank you, Dr. Wagner. I am not sure that anyone has left any implication on whether mucus is a desirable or an undesirable side-effect.

We have another question which has been handed to Dr. Dziuk to answer.

DR. DZIUK: The question is:

How did you establish that the fertility failures you have reported associated with MAP treatment were due to impaired sperm transport?

First of Wisconsin takes credit for the question and he wants me to take credit for the answer, I guess.

The treatments that we used were high levels of progesterone followed by HCG, then flushing the eggs out of the oviduct and noticing if they were fertilized and if sperm were present. The eggs appeared to be perfectly normal and, if the animals showed heat, that is, they had enough endogenous estrogen, then we got fertility. And when we gave estrogen, we did get sperm transport and fertility.

We also gave estrogen to pigs that we did not give HCG to, so there was no ovulation and no eggs there, and we could recover sperm. However, we could never recover sperm from those animals receiving HCG which did not show heat and we did not get fertilized eggs up there. We did not get sperm in the oviduct. Now we got motile sperm in the uterus as long as 48 hours after insemination in these pigs that ovulated but did not show heat. We found that when the eggs went down into the uterus, they could pick up the sperm down in the uterus even 48 hours after they had been ovulated, but, of course, then it is too late as far as the egg is concerned. We gave the HCG, no estrogen, and we got eggs, no sperm, no
sperm in the oviduct, no sperm on the eggs. Then we gave estrogen and we got sperm on the eggs and reasonable fertility. Then we gave estrogen without the HCG, so the estrogen is there, and we got sperm in the oviduct with no eggs. So that maybe the estrogen in some way enhances the capacitation as Dr. Casida mentioned, but my guess is that it is probably pretty simply transport, at least to start with. They have to be there anyway whether they are capacitated or not.

Have you taken control animals and treated animals and attempted to recover or quantitate the recovery of sperm from the oviducts in both so that you know pretty definitely that they are or are not being transported?

DR. DZIUK: Note these eggs were recovered 14-24 hours after ovulation at which time they should have been fertilized and should have a reasonable number of sperm on the zona pellucida. You do not find any sperm and, in these animals in which we did not get fertility, there are no sperm there at all and none in the oviduct that we could recover by any means.

DR. FIRST: I still raise the question with you in view of the difficulty of sperm recovery from the oviduct that, because you do not find the sperm in the egg, does not necessarily mean that they were not in the oviduct.

DR. DZIUK: No, not necessarily, but when we can give estrogen and get sperm in the oviduct and sperm on the eggs, then there is at least circumstantial evidence, and it satisfies me.

DR. DAVID POPE of British Drug Houses: I would like to know if anybody here has run into this with numerous cows, both in beef and dairy herds.

DR. MARION: There is no further comment. One other comment on that, in some of our cattle, we found most of them came in heat at 10 'oclock at night. If they are only going to stay in heat eight hours, as some of our synchronized animals did, they would not stand for a bull during the normal time in which you are checking for heat.

DR. CARNAHAN of Kansas State: I have noticed, on both a beef herd and on a dairy herd that a portion of the cows that have not conceived after treatment go into anestrus. After a period of three or four months, they then start silent cycling or development of some follicles. A little later some of these cows develop corpora lutea and, after a time, they finally come back into normal cycling and apparently normal conception. I have run into this with numerous cows, both in beef and dairy herds.

DR. CASIDA: Is there the implication here of a delayed effect for perhaps two or three months after treatment?

DR. CARNAHAN: There is an implication that there is a nonbeneficial effect for up to six months. Usually you do not see this anestrus for about two months after removal from treatment. Then I have run into trouble with these cows and have not had success whatsoever with any hormone I have tried.

DR. CASIDA: One further question. Have you seen this in situations of a controlled experiment? So you have a good reason to believe that it is actually more frequent in treated animals than in quite comparable animals that have not been treated, but at the same period of time in life, season and so forth?

DR. CARNAHAN: Yes, I think Dr. Marion can help on this in some of the herds of cattle they had there at K-State. The other, the beef herd that I mentioned, all cattle were treated, so I couldn't. I don't believe he treated all of the cattle all of the time, did you?

DR. CASIDA: Have you a comment, Dr. Marion?

DR. MARION: There is no further comment.

DR. SORENSON: This morning Dr. Hansel made a statement concerning the cattle at the Briarcliff Farm that had calves on them at the time of the start of the experiments. When
they were taken off experiment, they started cycling in a short time.

I wanted to ask him if he thought this was due to corpus luteum or was it due to the lack of oxytocin being stimulated by these calves suckling. He mentioned these were crossbred animals. Our experience has been with anything that has Indian breeding in it, you mentioned Charollais, but we do not have any Charollais in the United States, except maybe one or two here and there. They are Charollais, mostly, perhaps, but most of them still have Brahman blood in them. We have found that our Brahman crossbred calves may nurse three and four times as many times a day as our European breeds. And therefore we have a great deal of difficulty in our Gulf Coast regions where we have a preponderance of these crossbred cattle of getting cattle to come back into estrus while they are suckling a calf. The minute the calf is weaned the cattle will be in heat in about a week. But I wanted to pose this question to you: Is this oxytocin or is it the corpus luteum?

DR. HANSEL: Of course, I don't really know. I would certainly like to look into the possibility of oxytocin.

Actually, I do not separate the two effects in my own mind. I do not know how far to go back to start answering this question.

We are fairly well convinced that oxytocin does cause the release of LH now, and we are also fairly well convinced that the LH is luteotropin in the cow, so it could well be failure of the corpus luteum that still involves LH. We will present the data for these rash statements a little later.

DR. DONALDSON Australia via Cornell: I would like to comment on the anestrus in the Brahman crossbred cattle while the calf is suckling.

We have had the same experience in Australia in crossbred and also in purebred cattle that show the British breeds. So I would not like to see the crossbreds implicated as being the sole victims of this phenomenon.

And we feel that nutrition is playing an extremely important part in this suckling effect.

DR. SORENSON: I will agree with that.

DR. DONALDSON: Thank you.

DR. SORENSON: European cattle on poor nutrition won't do it.

DR. CASIDA: Dr. Wagner this morning you mentioned that in attempts to synchronize the post-partum ewe the success with the non-lactating ewes was poorer than with the lactating. Have I indicated that correctly?

DR. WAGNER: Yes and no.

DR. CASIDA: All right. For the moment I am going to accept that you have said yes so I can ask the question. All indications that we have found in cattle and in swine, and to some extent in sheep, are that early weaning may cause various ovarian abnormalities and I believe if you weaned your lambs at four weeks, the time of attempted synchronization was super-imposed on a period of roughly the peak of lactation. Is that correct?

DR. WAGNER: That sounds pretty close.

In reference to this question, I think it should be pointed out, one, that we were surprised at the response we got and that we have had better results in other dry ewes.

This would not be quite the same group of animals because often times they are dry because they have lambed early in the spring and they have been dried for a long time.

In reference to this particular experiment, they were weaned, and again I am guessing, at three to four weeks after lambing. This would vary, of course, in the group, but equal in both groups, and a two-week period followed before the beginning of treatment and then a 16-day period plus a couple of more days before they were in heat, so you have approximately 30 some days after weaning before they are given the first PMS and bred.

Also, my question to you would be whether this abnormality in the polyestrous animal such as the pig and the cow that you see after early weaning, would carry over to the ewe which we would assume is anestrous whether she is lactating or not in the spring?

DR. CASIDA: Fortunately this is the kind of meeting in which we are not expected to answer the questions. We speculate and raise questions for further study.

So thank you, Dr. Wagner.

Well, gentlemen, we have reached the end of this portion of the program. I appreciate very much the way you have helped during this discussion period,