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EFFECT OF NOR-ETHISTERONE AND PREGNANT MARE SERUM ON ESTRUS
AND FERTILITY IN AWASI EWES

By

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Hormone Treatment in Sheep

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ABSTRACT

Two trials were conducted on 89 fat-tailed Awasi ewes at the Agricultural Research and Education Center of the American University of Beirut during the year 1963. The study was designed to determine the effect of orally administered nor-ethisterone and PMS on the synchronization of estrus, fertility, twinning rate, birth weights, gestation periods and possibilities of using these compounds to produce three lamb crops in two years by inducing estrus and ovulation in non-cycling ewes. In the first trial 62 adult ewes were divided into a control group and 10 and 20 mg. progesterone treatment groups; one-half of the treated ewes in each group was injected with 500 I.U. of PMS 48 hours after cessation of nor-ethisterone feeding. The second trial was conducted using 11 adult ewes and 16 ewe lambs. Dosage levels of 30, 40 and 50 mg. of nor-ethisterone were used and all ewe lambs were injected with 500 I.U. of PMS 48 hours after the progestational treatment.

Nor-ethisterone in doses of 10, 20 and 30 mg. daily was ineffective in completely inhibiting estrus in the ewes whereas dose levels of 40 and 50 mg. were adequate. 100 percent of the adult ewes fed 40 mg. of nor-ethisterone without an injection of PMS exhibited synchronous estrus during days 1-5 and 18-22 post-treatment which corresponds to the first five days of the first and second estrus cycles, respectively.

Dosage levels of 10, 20 and 30 mg. resulted in poor synchronization. Supplementation of the pretreatment with an injection of PMS tended to group the estrus during the first five days of the post-treatment period. No synchronization of estrus was obtained during the first and second post-treatment estrus cycles with a dose level of 50 mg. which appeared to be an overdose.

During the first five days of the post-treatment period, 25 percent of the treated ewe lambs exhibited estrus although all received an injection of 500 I.U. of PMS; none of these ewe lambs conceived. This study indicated that nor-ethisterone had a retarding effect on the puberty and conception of ewe lambs. However these observations further indicated that regardless of whether nor-ethisterone was given to mature ewes or ewe lambs, the average conception rate (54.5 and 0.0 percent, respectively) was significantly lower in these groups than in the control ewes (76.5 percent). During the two trials there were no multiple births among the treated ewes indicating a possible adverse influence of nor-ethisterone treatment on fertility. The birth weights of lambs from treated ewes were not affected.

It appeared from the results of this study that coincident estrus and ovulation in anestrous and cycling Awasi ewes can be induced provided a pretreatment of nor-ethisterone, at adequate dose levels, is followed by an injection of PMS. Such a treatment would make the production of three lamb

crops in two years possible if the detrimental effect of
nor-ethisterone on fertility is negligible.

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INTRODUCTION

Production of extra-seasonal lambs for the early spring marketing is one of the major problems confronting sheep producers in the United States and other countries including the Middle East. Ewes of most breeds are receptive to the male only during the fall producing a lamb crop in the spring. The production of an early or late lamb crop requires the ewes to be bred at times other than the normal breeding season. Merino, Dorset Horn and Rambouillet ewes have a shorter anestrous period than most other breeds and can be bred to produce extra-seasonal lambs. The local fat tailed ewes of Lebanon (Awasi breed) also appear to be able to breed throughout most of the year.

In the past, the livestock and sheep breeders have been attempting to control the breeding pattern of their farm animals through management practices so that they may be bred during a definite period of the year for economic and certain managerial advantages. Attempts on the part of the shepherds to breed their sheep along a specific pattern in the remote past have been recorded in the book of Genesis of the Holy Bible.

Success in breeding sheep out of season will open a field for studying possibilities of obtaining more than one lamb crop per year. In the past decade investigations by several research workers have demonstrated a reasonable degree

of success in controlling the dates of breeding and lambing in sheep by estrus synchronization. The induction and control of estrus in sheep could prove to be a useful tool to the sheep industry and have the following advantages: (1) facilitates widespread use of artificial insemination thus providing the breeder an opportunity to increase the use of outstanding fertile rams; (2) provides managerial advantage by restricting the lambing time to a few days; (3) provides opportunity for marketing a homogeneous lamb crop to the best advantage of the producer; and (4) provides opportunities for breeding sheep out of season and fixing breeding programs according to the market demands. Bringing the entire flock into heat at one time may create a problem of ram-power but artificial insemination can be an answer to this problem. Deep frozen or fresh semen can be used without lowering the fertility to any appreciable extent. Fertility is one of the many factors on which the economic production from a sheep enterprise depends. The increased ram requirement can be overcome by synchronizing the estrus of a reasonable number of ewes in each successive group.

Successful production of synchronous estrus and coincident ovulation in a reasonable percent of ewes was not obtained until the investigations of Robinson (1952) and Dutt (1953) which disclosed the importance of a series of progesterone injections preceding an injection of PMS. Later investigations by other workers confirmed the usefulness of

progesterone pretreatment followed by a PMS injection. Recently orally effective progestational compounds have become available and it has been shown that they are as effective in controlling estrus and ovulation as injections of progesterone. Feeding of an orally active progestational compound has the obvious advantage of less handling thus lowering the labor cost of the treatment. Moreover, progesterone feeding has less residual effect than injections of progesterone.

The purpose of this study was to determine the effect of feeding an orally active progestational compound, norethisterone (Primolut N Schering), on the estrous cycle and subsequent fertility in a flock of Awasi sheep. It also involved the study of the effect of this treatment on the twinning percentage, birth weights of lambs, gestation periods and to examine the possibility of using this drug to produce three lamb crops in two years by stimulating ewes to come into estrus at times when they are not normally cycling.

REVIEW OF LITERATURE

Dutt et al. (1948) studied the alteration of the estrual cycle in sheep by using progesterone in daily injections of 5 mg. and 10 mg. per ewe per day for a period of fourteen days and observed that estrus and ovulation was effectively synchronized by a daily injection of 10 mg. crystalline progesterone for fourteen days in 100 percent of the cycling ewes, while it was effective only in 67 percent of the ewes on lower dosage levels. They further observed that average interval from the end of progesterone treatment to the onset of the next estrus for 5 mg. and 10 mg. daily dosage levels was 2.8 days with a range of 2.0 days, and 3.2 days with a range of 0.5 days, respectively.

Cole et al. (1945) studied the effect of supplementing PMS with progesterone or progesterone and estrogen on the induction of estrus in anestrus ewes. This work showed that when 500 R.U. of estrogen were given 16 days and 300 mg. progesterone 13 days before the initial injection of 450 I.U. PMS, followed 17 days later by a second injection of 450 I.U. PMS, 75 percent of anestrus ewes exhibited estrus, whereas only 42.9 percent of the ewes came into heat after two injections of 450 I.U. PMS alone. None of the ewes exhibited estrus in the control group.

Of the ewes receiving 450 I.U. PMS supplemented with 300 mg. progesterone 33.3 percent exhibited estrus as compared

to 27.3 percent receiving PMS alone. When both PMS and progesterone were given, 55.4 percent conceived as compared to 16.7 percent receiving PMS alone. The combined treatment with an androgen (testosterone propionate) and PMS induced estrus in 81.2 percent of the ewes as compared to 44.9 percent of those receiving PMS alone.

Robinson (1950) in his studies on sheep used PMS or stilbestrol alone or in combination to induce pregnancy in anestrus ewes concluded that ovulation without heat can regularly be induced in Hampshire and Suffolk ewes with a mean ovulation rate of 2.8 eggs by injecting 800 I.U. PMS. He suggested that spontaneous ovarian activity may modify the effect of PMS in two ways, (a) Corpus Luteum active - ovulation may be entirely suppressed or delayed for up to nine days and ovulation is associated with heat, and (b) Corpus Luteum waning - ovulation is usually somewhat delayed and is accompanied by heat.

Robinson (1952) conducted experiments on ewes in deep anestrus to determine the effect of hormone treatment in inducing estrus. 1000 I.U. PMS alone or in combination with 35 mg. progesterone injected 48 hours prior to PMS injection were used. A response which closely approached physiological normality was obtained when progesterone was injected subcutaneously in oil, followed 48 hours later by 1000 I.U. PMS. This treatment procedure resulted in estrus with coincident ovulation and fertilization in 42.9 percent of the anestrus

ewes.

When progesterone was administered in 50 percent ethanol and injected subcutaneously or intravenously 48 hours prior to PMS injection, the ewes ovulated without estrus. These observations indicated that a pretreatment sometime before an injection of PMS and slow absorption of progesterone are necessary to condition the animal to respond physically to ovarian estrogen. Pretreatment with progesterone earlier than 48 hours before an injection of PMS is therefore recommended.

Robinson (1953-54) conducted two experiments. The first experiment involving sixty yearling ewes and the second experiment involving eighteen mature ewes were all within deep anestrous. The ewes receiving PMS alone ovulated without estrus. 88.9 percent of the yearling ewes and 50 percent of the adult ewes receiving two daily injections of 12.5 mg. progesterone per ewe for three days followed 48 hours later by a single injection of 1000 I.U. PMS exhibited estrus and ovulation. The onset of heat was quite dramatic starting 24 hours after PMS injection and all ewes were served within 36 hours after treatment. Those receiving a daily dose of 25 mg. progesterone per ewe for three consecutive days or a single injection of 75 mg. progesterone followed by 1000 I.U. of PMS were less effective than PMS alone in inducing estrus; incidence of estrus being seven and four out of twelve, respectively.

The hysterectomized and intact ewes responded in a

similar manner suggesting that the conditioning effect of progesterone is mediated via the central nervous system.

Dutt (1953) studied the effect of progesterone injections prior to PMS on the induction of estrus in anestrus ewes. The treatments were 500 I.U. PMS injected alone, or 500 I.U. PMS injected after 1, 2, 3, 4 or 5 injections of 30 mg. progesterone at three day intervals. He observed that although none of the ewes receiving PMS alone exhibited estrus during the experimental period, all had ovulated. Four out of nine (44.4 percent) receiving progesterone alone showed estrus and had ovulated. All ewes in the group receiving five injections of 30 mg. progesterone, each injection followed by PMS injection, exhibited estrus and ovulated. The remaining treatment groups receiving 1-4 injections of 30 mg. progesterone followed by a PMS injection also had ovulated but not all ewes showed coincident estrus.

Observations showed that 49 percent of the ova recovered from all groups were fertilized and Dutt concluded that ova shed in anestrus ewes by progesterone treatment followed by PMS injection are fertilizable.

Gordon (1958a) conducted preliminary field trials on two groups of Welsh Mountain ewes using PMS in conjunction with progesterone in an attempt to increase flock fertility and extra-seasonal production of lambs. The first group with 25 ewes and the second with 33 ewes were given three injections of 30 mg. progesterone at 2-day and 3-day intervals, respec-

tively followed 48 hours later by an injection of 750 I.U. of PMS. 100 and 99.9 percent of the treated ewes in the respective groups showed estrus within a 6-7 day post-PMS-injection period. The incidence of estrus in the control group was scattered over the entire 16 day treatment and post-treatment period.

This work further indicated that conception rate in the first group (25 ewes) was not different from that of controls while in the second group (33 ewes) the conception rate to first service was lower than the controls though the difference was not statistically significant. With repeat services conceptions in these groups increased over the controls.

Gordon (1958b) in his field trials on flocks of sheep over a period of four years using various combinations of progesterone and PMS found that the estrus response varied from 31.8 to 90 percent with different dosage levels. Conception rate was normal in non-lactating ewes after induction of estrus, but below normal in ewes at the peak of their lactation.

Gordon noted that three out of four suckling ewe lambs came into estrus and one ovulated following progesterone-PMS therapy. A 4-cell ovum was recovered from this 70-day-old animal. These observations indicate that autumn lambings do not tend to reduce subsequent breeding performance in ewes (that is, mated to lamb the next spring).

McDonald (1961) conducted an experiment on ewes in deep anestrus to study the effects of progesterone and PMS separately and in combination on induction of estrus and changes in ovaries and genital tract. Ten ewes served as controls; thirty-five received progesterone injections of 80 mg. daily for 4 to 12 days; ten received 750 I.U. of PMS injection alone; while fifteen received progesterone injections for 4 to 6 days followed by PMS.

Recently weaned ewes treated with progesterone alone neither ovulated nor exhibited estrus; 60 percent of those given PMS alone ovulated without showing estrus; all ewes in which progesterone treatment was followed by a single injection of PMS ovulated, but only one out of fifteen (6.6 percent) exhibited estrus.

Combs et al. (1961) fed 120 mg. of provera (6-methyl-17-acetoxypregesterone) per ewe per day in half a pound of ground grain once daily for 13 days to 81 cycling ewes. 92.6 percent of the treated ewes exhibited estrus from the third to the fifth day after cessation of progesterone feeding. First service conception rates for different groups of ewes were 91.7, 44.8, 90, 70, 40 and 30 percent with an average of 58 percent. Lowest conception rates were noticed in the largest breeding group of 29 ewes and in the two small groups served by yearling rams for which there had been no fertility check.

It was noticed that ewes not conceiving at the first service were still synchronized and most of them conceived at

the second service. Only five ewes from the group of 29 ewes failed to conceive at the second service. These workers concluded that the conception rate to some extent depended upon the fertility of the ram.

Hinds et al. (1961 and 1962) conducted preliminary experiments on 88 cycling ewes attempting to synchronize their estrus by the use of different levels of MAP (6-methyl-17-acetoxyprogesterone), a synthetic progesterone compound. The dosage used was 0, 75 and 100 mg. of MAP once daily in half-pound concentrate mixture for 14 days. The results showed that on an average 88.4 percent of the ewes fed 75 mg. and 100 mg. MAP per ewe per day (81.8 and 95.2 percent for the 75 mg. and 100 mg. treated groups, respectively) showed estrus within the first five days post-treatment as compared to 38.6 percent of the controls. Laboratory examination indicated that the actual consumption of MAP per ewe per day was only 58 mg. and 75 mg. respectively for the treated groups instead of the planned consumption of 75 mg. and 100 mg. per group.

For further experimentation the ewe flock was divided into the following groups, (1) 80 ewes in groups of 20 were fed individually 0, 25, 50 and 75 mg. MAP daily for 14 days, (2) 69 ewes received 50 mg. MAP each for 14 days in one pound of ground corn, (3) 25 ewes served as control and (4) 58 ewes received 75 mg. MAP daily for 14 days in one pound of ground corn. The results obtained were similar to those of the previous experiment.

These data indicated that daily consumption of as little as 25 mg. MAP when individually fed and 50 mg. of MAP when group fed gave reasonable synchronization of estrus. Evidence further indicated that yearling ewes responded equally as well as older ewes provided they consumed regularly the daily dose of progesterone in the feed. No detrimental effects on breeding capacity of ewes in the next breeding season were noticed.

Evans et al. (1962a) in two trials studied the effect of feeding MAP on the estrus cycle and subsequent fertility in ewes. In the first trial, they fed to 35 ewes in all stages of estrus cycle 50 mg. doses of MAP per ewe in corn meal daily for 14 days. None of the treated ewes exhibited estrus during the treatment period. No post-treatment injection of PMS was given. 82.8 percent of the treated ewes exhibited estrus within 8 days post-treatment with an average of 3.14 days.

In the second trial 40 ewes were divided into groups fed 60 mg. and 90 mg. of MAP for 15 and 18 days, respectively. Estrus was synchronized in an average of 95 percent of the treated ewes (90 percent with 60 mg. group and 100 percent with 90 mg. group) within 2-5 days post-treatment. Estrus was exhibited in all treated groups on an average of 3.2 days after the cessation of progesterone treatment. However for the 60 mg.-15-day-treatment group the average was 2.8 days and for the 90 mg.-18-day-treatment group the average was 3.6 days.

42.1 percent of the ewes in first trial and 84.2 percent in the second trial conceived to the service of the first post-treatment estrus.

Evans et al. (1962b) conducted two trials to induce breeding activity in anestrus ewes. In the first trial two groups of 20 ewes each were fed 50 mg. MAP per ewe per day for a period of 7 days and 14 days respectively followed 48 hours later by 500 I.U. of PMS. Synchronous estrus was exhibited by 25 and 65 percent of the ewes in 7-day and 14-day-treatment groups, respectively. The lambing percentage was 30 and 40 percent respectively for the 7-day and 14-day-treatment groups.

In the second trial 50 ewes were divided into five groups of ten ewes each. Groups 1 and 2 were fed 75 mg. of MAP per ewe per day for 14 days and 21 days, respectively; groups 3 and 4 were fed 1 mg. of CAP (6-chloro-6-17-acetoxyprogesterone) per ewe per day for 14 and 21 days, respectively; and group 5 served as the control. Ewes in groups 1 and 3 and groups 2 and 4 were injected 48 hours and 72 hours after cessation of progesterone feeding with 500 and 1000 I.U. of PMS, respectively.

Synchronization of estrus was observed in 10, 40, 10 and 20 percent of ewes in groups 1 through 4, respectively. None of the control ewes exhibited estrus. The CAP treated groups 3 and 4 had a significantly higher ovulation rate than the MAP treated groups 1 and 2, but the fertility did not

differ significantly between the four treated groups.

Hogue et al. (1962) in an attempt to synchronize estrus in cycling ewes fed provera (6-methyl-17-acetoxypregnesterone) in 60 mg. daily doses mixed with 0.2 lb. of soya bean oil meal per ewe per day to 40 ewes for 20 days. No PMS was used. 92.5 percent of the treated ewes exhibited synchronized estrus within 64 hours after the end of treatment. Conception rate noted in 18 naturally bred and 19 artificially bred ewes was 61 and 16 percent, respectively. The conception rate was 50 and 49 percent respectively in the naturally and artificially bred groups after normal estrus without treatment.

It was also observed that several of the ewes in the naturally-bred-synchronized estrous group showed estrus and were remarked during the 30 days after the first mating but the lambings corresponded to the first matings. It was concluded that 60 mg. provera per ewe per day for 20 days was appropriate for synchronizing estrus and maintenance of reasonable fertility in the cycling ewes.

Botkin (1963) in a study of synchronization of estrus fed provera mixed with grain for a period of 14 days to 250 ewes. Synchronous estrus was exhibited by about 90 percent of the ewes and a conception rate of about 70 percent at first service was obtained. He further observed that the ewes which did not conceive at first service came in to heat again after about 17 days.

Under a similar trial with range ewes fed provera added to protein blocks, synchronization was achieved in about one-half of the 100 ewes which were bred naturally.

Botkin et al. (1963) in experiments covering three years data with 325 ewes fed synthetic progestational compounds in grain mixtures for 14 days before breeding. 89.2 percent of the treated ewes were marked within the first five days following the cessation of progesterone feeding. Ewes failing to conceive at the first synchronized estrus were still synchronized at the second estrous cycle. 55 percent of the synchronized ewes conceived at first service, 31 percent at second service and 4 percent at the third service. Of the unsynchronized ewes, 42 percent lambed during the third lambing period. It was observed that twinning percentage was slightly reduced in the ewes fed progestational compounds especially in the Suffolk breed.

Southcott et al. (1962), in a preliminary trial feeding provera in different dosage levels of 0, 6.6, 20 and 60 mg. daily for 14 days in gelatin capsules, noticed that orally fed provera in 60 mg. daily doses was effective in synchronizing estrus in 100 percent of the treated ewes with a conception rate of 70 percent. Lower doses reduced the incidence of estrus during treatment but did not completely prevent it. The conception rates for the controls, 6.6 mg. and 20 mg. dose treatment groups were 70, 70 and 60 percent, respectively.

In the second trial 100 ewes, divided into five groups, were given 50 mg. provera per ewe per day orally for 17 days alone or followed 24 hours later by 500 I.U. of PMS and 48 hours later by 600 I.U. of HCG (Human Chorionic Gonadotropin). These five groups were compared with those treated with subcutaneous injections of 10 mg. crystalline progesterone every alternate day for a similar period alone or followed by similar PMS and HCG injections. These data indicated that all treatments produced an appreciable synchronization of estrus. The results obtained with provera fed orally and crystalline progesterone injections were similar. Conception rate following mating within 6 days after end of the treatment was 51.7 and 37.9 percent for the oral provera feeding and injected progesterone treatments respectively. The higher conception rate with oral administration was probably due to a smaller residual effect than was in the case of the injection of crystalline progesterone.

It was found that the use of PMS following progesterone treatment did not result in any multiple births nor improved fertility.

Pursel and Grahm (1962) conducted a trial with sixty anestrous ewes in different groups using crystalline 6-methyl-17-acetoxypregesterone orally in doses of 10 mg., 30 mg. and 60 mg. in aqueous drench and 30 mg. mixed in concentrate mixture fed once daily for a period of 12 days followed 48 hours later by a subcutaneous injection of 25 mg. of FSH

The control group was also administered 25 mg. of FSH. It was observed that 17.6 percent of the control (10) ewes exhibited estrus in 3 days following an injection of 25 mg. FSH but only one ewe was pregnant at slaughter. Estrus synchronization was exhibited by 70, 75 and 75 percent of the ewes receiving oral progesterone doses of 10 mg., 30 mg. and 60 mg., respectively. The ewes exhibited estrus on the first or second day after injection of 25 mg. FSH. Of the ewes mated, 28.6, 0.0 and 50 percent conceived in the respective groups.

100 percent of the ewes fed 30 mg. of progesterone in the concentrate mixture for 12 days followed 48 hours later by a single injection of 20 mg. FSH exhibited estrus during the first 2 days following the injection of FSH and 44.4 percent conceived.

Brunner et al. (1964) used oral MAP and PMS injections in different combinations to test their effects on estrus synchronization and fertility of both normally cycling and anestrus ewes. It was concluded that MAP alone was ineffective in synchronizing estrus in anestrus ewes. For the normally cycling ewes 60 mg. of MAP per ewe given orally for 20 days was more effective than 30 mg. per ewe for 16 days, both in synchronizing estrus and maintaining the fertility of the ewes.

Four combinations of MAP and PMS were tested on ewes at the beginning of their normal cycling periods. All the

tested combinations were reasonably successful. One hundred percent synchronization and 82 percent fertility were observed with a treatment including 750 I.U. of PMS injected 6 days before, and one day after an 8-day MAP feeding period.

From this study, these workers concluded that MAP in daily doses of 60 mg. for 20 days followed by a single injection of PMS successfully synchronized estrus in sheep and maintained their fertility, while MAP alone was ineffective.

Zimbelman (1963) conducted experiments feeding 0, 20, 40 and 60 mg. levels of MAP and 0.4, 0.8 and 1.6 mg. levels of MGA (melengestrol acetate) per ewe per day for a period of 15 days. Estrus was inhibited in all ewes receiving orally 60 mg. of MAP and at all the three levels of MGA. With 0.4 mg. MGA only 55.5 percent treated ewes exhibited estrus with ovulation within 7 days post-treatment; while 27.7 percent ovulated without estrus during this period but showed estrus between 20 and 24 days post-treatment. First service conception rate of synchronized ewes of this group was 75 percent. All ewes receiving 0.8 and 1.6 mg. MGA were not effectively synchronized as minimum number of ewes exhibited estrus during the first 20 days post-treatment. The conception rates of these groups were lowest in the treatment groups.

These observations indicated that 0.4, 0.8 and 1.6 mg. levels of MGA were overdosages and were not effective in

completely synchronizing estrus.

Addleman et al. (1963a) fed 50 mg. progesterone (repromix) per ewe for 16 days during the anestrus period of early summer. PMS was injected at the rate of 4 R.U./lb. body weight on the fourteenth day to one group and on the sixteenth day of treatment to the second group. From this work it was concluded that in breeds of sheep which are noted for their late spring lambing tendency hormone treatment may be advantageous. These ewes can be brought into estrus earlier. PMS is essential for the production of fall lambs because of its stimulatory effects on ovulation.

Addleman et al. (1963b) used repromix orally at the rate of 50-60 mg. per ewe per day for 14-16 days during normal breeding seasons. It was observed that approximately 80 percent of all the treated ewes in 1961 and 97 percent during 1962 were bred within 8 days following cessation of progesterone feeding, while control ewes were bred during the first 16 days of the breeding season. 47 percent of the bred ewes lambed in 1962 and 77 percent lambed in 1963 during the first 8 days of the lambing season, whereas only 40 percent of the bred control ewes lambed during the first 8 days of the lambing season. 14.1 and 13.4 percent in 1962 and 1963 respectively showed two heat periods following progesterone treatment but lambed from matings during first estrus.

It was concluded that orally administered progesterone appears effective for synchronizing estrus in ewes

although a slight upset in the hormonal balance from orally administered progesterone has been reported.

MATERIALS AND METHODS

Local fat-tailed sheep of the Awasi breed from a flock maintained at the Agricultural Research and Education Center of the American University of Beirut were used for the present study. The study was conducted in two experiments; the first trial involving mature ewes two years of age and older, while in the second trial, sixteen out of twenty-seven ewes were ewe lambs with an average age of eight months.

In both trials harnessed rams were used to mark and breed the ewes in heat to ascertain the date of breeding. The ewes were checked twice daily for ram marks.

Hormone Preparations

Nor-ethisterone (trade name Primolut N, Schering AG Berlin): Since the most commonly used orally effective synthetic progestational compound, provera, (6-methyl-17a-acetoxyprogesterone) could not be procured from the United States due to export restrictions on drugs still under test, a synthetic progestational compound nor-ethisterone (17a-ethynyl-19-nor-testosterone) in the form of 5 mg. tablets was used. Nor-ethisterone when administered orally is eight times more potent than crystalline progesterone injection in women (White et al., 1959).

Pregnant Mares' Serum (PMS): A freeze-dried product of Schering AG Berlin (trade name Anteron) dissolved in distilled water immediately before injection into ewes was used

for stimulation of ovulation.

Experiment 1

The first preliminary trial commenced on May 11, 1963. One month prior to this experiment an aproned ram was placed in the flock to mark the ewes that were in estrus. No ewe was marked during one month prior to the start of the experiment. The breeding data of the Agricultural Research and Education Center of the American University of Beirut flock for the years 1954 through 1963 reveals that some of the Awasi ewes have been cycling during the months of May and June as 26 out of 374 ewes (6.95 percent) gave birth to lambs during the months of October and November during the past nine years.

The experiment consisted of sixty-two ewes who were randomly assigned to four experimental groups and a control group. Each treatment group consisted of twelve ewes while the control group contained fourteen ewes. The ewes in the different groups were marked for identification by placing different colors on their heads with grease pencils. These color markings were renewed periodically to insure that the groups could be distinguished.

Throughout this trial, the ewes were maintained on pasture with all groups in one flock. The sixty-two ewes were divided into treatment groups as follows:

Group 1 - controls.

Group 2 - 10 mg. nor-ethisterone per ewe per day for 12

- days followed 48 hours later by 500 I.U. PMS.
- Group 3 - 20 mg. nor-ethisterone per ewe per day for 12 days followed 48 hours later by 500 I.U. PMS.
- Group 4 - 10 mg. nor-ethisterone per ewe per day for 12 days.
- Group 5 - 20 mg. nor-ethisterone per ewe per day for 12 days.

The nor-ethisterone tablets used were administered orally once a day. The hormone tablets were administered between 1:00 p.m. and 2:00 p.m. daily before the ewes were taken to pasture for the afternoon grazing.

The ewes were allowed to be bred and marked during twelve days of hormone feeding and twenty-two days of the post-treatment period.

Experiment 2

The second trial was started on September 15, 1963. In this trial there were twenty-seven ewes of which sixteen were ewe lambs about eight months old. The ewes were randomly assigned to four treatment groups. First the mature ewes were randomized into the four different groups then the ewe lambs were randomized to be sure that each group had equal number of them. The ewes were then divided into two major groups to reduce the amount of labor required to check each ewe and to avoid having to handle each ewe daily. The ewes were fed barley hay ad libitum and were allowed an additional concen-

trate mixture ration of one-half pound per ewe per day.

The four treatment groups were as follows:

Group 1 - controls.

Group 2 - 30 mg. nor-ethisterone per ewe per day for 12 days.

Group 3 - 40 mg. nor-ethisterone per ewe per day for 12 days.

Group 4 - 50 mg. nor-ethisterone per ewe per day for 12 days.

The hormone tablets were administered orally once a day between 7:00 a.m. and 7:30 a.m.

The four ewe lambs in each group were injected with 500 I.U. PMS intramuscularly 48 hours after the final dose of nor-ethisterone.

A harnessed ram was left in each group throughout the experiment to mark those bred. The rams were kept with the ewes for 40 days after treatment.

RESULTS AND DISCUSSION

Data for this study were taken from 89 Awasi sheep maintained at the Agricultural Research and Education Center of the American University of Beirut. The study was divided into two experiments conducted in May and September, 1963. Data for the first trial were taken from a flock of mature Awasi sheep while data for the second trial were taken from ewe lambs as well as mature sheep. The results are reported in tabular form in tables 1-5.

It has been established that ovulation without estrus could regularly be produced by injecting PMS (Robinson, 1950). A pretreatment of progesterone before injecting PMS is necessary to place the animal in a proper hormonal balance resulting in a better response to the ovarian stimulation (Robinson, 1952). Since this would more closely approach the normal physiological estrus in ewes better fertility should result.

Suppression of Estrus by Nor-ethisterone

In the first trial with a daily dose of 10 mg. of nor-ethisterone 12.5 percent of the ewes exhibited estrus during the treatment period of 12 days as compared with 42.9 percent of the control ewes (table 1). These observations indicate that feeding of nor-ethisterone at 10 mg. daily dose levels reduced the incidence of estrus but did not completely suppress it. The incidence of estrus with dosage levels of 20

Table 1 - Effect of feeding nor-ethisterone on the estrus cycle.

Experimental group	Daily dose of nor-ethisterone (mg.)	Duration of treatment (days)	Number of ewes	No. Ewes in estrus during treatment	%
Trial I					
Group 1	0	12	14	6	42.9
Group 2	10	12	24	3	12.5
Group 3	20	12	24	2	8.3
Trial II					
Group 1	0	12	7	2	28.6
Group 2	30	12	7	1	14.3
Group 3	40	12	6	0	0.0
Group 4	50	12	7	0	0.0

mg. of nor-ethisterone was 8.3 percent as compared with 42.9 percent for the control ewes. This dosage level did not completely prevent estrus in the ewes indicating that 20 mg. dose is also inadequate. These results were in agreement with those of Southcott et al. (1962) who reported that dose rates of 6.6 mg. and 20 mg. of provera were ineffective in preventing estrus in cycling ewes.

In the second trial, 14.3 percent of the ewes receiving a daily dose of 30 mg. of nor-ethisterone exhibited estrus as compared with 28.6 percent of the control ewes. The only ewe from the 30 mg. dosage group which showed estrus during the progesterone treatment exhibited it on the second day of the treatment. It is probable that this ewe was in the end phase of an estrus cycle when the treatment began. Except for this ewe, the 30 mg. dose level of nor-ethisterone completely suppressed estrus in the ewes. Zimbelman (1963) reported that estrus was not completely inhibited with MAP in dosage levels of 20 mg. and 40 mg. per day. It appeared from this study that nor-ethisterone had a stronger inhibitory effect on estrus than MAP.

At 40 mg. and 50 mg. daily doses of nor-ethisterone none of the ewes exhibited estrus during the treatment period of 12 days. These observations indicated that nor-ethisterone in dosage levels of 40 mg. and above seemed to be adequate to suppress estrus completely as none of the ewes on these doses showed estrus.

Estrus Synchronization

In the first trial the treatment groups 2-5 receiving daily dosage levels of 10 mg. and 20 mg. of nor-ethisterone with or without PMS injection did not show any significant synchronization during the first five days of the post-treatment period. However, during the first five days of the second post-treatment estrus cycle (18-22 days post-treatment) some synchronization of estrus occurred in the treated ewes, especially in the treatment groups 4 and 5 which did not receive any PMS injection. This indicates that the ewes fed 20 mg. of nor-ethisterone without PMS appeared to be still synchronized at the second post-treatment estrus cycle (18-22 days post-treatment).

The incidence of estrus during the first five days post-treatment was 33.3, 18.2, 33.3, 18.2 and 16.7 percent in treatment groups 1, 2, 3, 4 and 5, respectively (table 2). The differences between the treatment groups were not statistically significant. Similarly 11.1, 18.2, 25.0, 27.3 and 50.0 percent of the treated ewes in the respective groups exhibited estrus during the first five days of the second post-treatment estrus cycle (18-22 days post-treatment). Difference in the percent ewes showing synchronous estrus between the controls (11.1 percent) and 20 mg. treatment group without PMS (50 percent) was just below the level of significance ($P = 0.05$). Whereas this difference may not have been statistically significant it may be of biological significance.

Table 2 - Incidence of post-treatment estrus after nor-ethisterone feeding (trial I).

Experimental group	Treatment nor-ethisterone	No. of ewes	% ewes in estrus	
			I cycle (days) 1-5	II cycle (days) 6-17
1	Controls	9	33.3	44.4
2	10 mg. + PMS (500 I.U.)	11	18.2	27.3
3	20 mg. + PMS (500 I.U.)	12	33.3	33.3
4	10 mg.	11	18.2	36.4
5	20 mg.	12	16.7	16.7

11.1

18.2

25.0

27.3

50.0

It appeared from this study that the synchronizing effect of oral nor-ethisterone at 10 mg. and 20 mg. daily doses is slight. These observations are in agreement with Jochle (unpublished data) who indicated that an effective dosage of nor-ethisterone in sheep is 1 mg. per 3 lb. body weight daily per ewe over a period of 10-15 days followed 48 hours later by an injection of 750-900 I.U. of PMS. Southcott et al. (1962) indicated that the minimal effective daily dose of 6-methyl-17-acetoxypregesterone for achieving a reasonable synchronization of estrus in ewes is 1 mg. per kg. body weight. Since in this study the average body weight of adult Awasi ewes was about 50 kg., the dosage levels of 10 mg. and 20 mg. of nor-ethisterone seem to be insufficient to induce synchronization of estrus in all ewes. The PMS level used in group 2 and 3 was also lower than recommended by Jochle (unpublished data). Also these data were inconsistent with the findings of Zimbelman (1963) who achieved synchronization of estrus in 44.4 percent of the ewes with 20 mg. daily dosage levels of MAP within the first three days of the post-treatment period.

It appeared from this trial that the synchronizing effect of nor-ethisterone treatment without PMS was extended to the second post-treatment estrus cycle. A higher percentage of the treated ewes, without PMS, showed estrus during the first five days of the second post-treatment estrus cycle than during the first five days of the first post-treatment

estrus cycle. However, when nor-ethisterone treatment was followed by an injection of PMS greater synchronization of estrus was manifested in the first post-treatment estrus cycle. The observations in the present trial disagreed with the findings of Hinds et al. (1962) who observed that daily consumption of as little as 25 mg. of MAP, when individually fed to ewes, gave a reasonable synchronization of estrus. Pursel et al. (1962) also achieved estrus synchronization in 70 and 75 percent of the ewes receiving crystalline 6-methyl-17-acetoxypregesterone in daily doses of 10 mg. and 20 mg., respectively (the progesterone treatment was for 12 days and was followed 3 days later by an injection of 25 mg. FSH). It appeared that 6-methyl-17-acetoxypregesterone is a better progestational compound than nor-ethisterone for synchronization of estrus in ewes.

In the second trial 14.3 percent (1 ewe lamb) and 50.0 percent (1 adult and 2 ewe lambs) of the treated ewes receiving daily doses of 30 mg. and 40 mg. respectively showed estrus during the first five days of the post-treatment period. None of the control ewes or those on 50 mg. dosage level exhibited estrus during the entire first post-treatment estrus cycle of 17 days (table 3). Partial synchronization of estrus with the 40 mg. daily dose of nor-ethisterone was statistically significant ($P = 0.05$). 16.7 percent of the ewes receiving 40 mg. of nor-ethisterone showed estrus during the first five days of the second post-treatment estrus cycle while 14.3 and

Table 3 - Incidence of post-treatment estrus after nor-ethisterone feeding (trial II).

Experimental group	Treatment* nor-ethisterone	No. of ewes	% ewes in estrus			
			I cycle (days) 1-5	II cycle (days) 18-22	III cycle (days) 23-34	III cycle (days) 35-39
1	Controls	7	0.0	14.3	28.6	14.3
2	30 mg.	7	14.3	0.0	0.0	14.3
3	40 mg.	6	50.0**	16.7	0.0	0.0
4	50 mg.	7	0.0	14.3	0.0	28.6

* There were 4 ewe lambs in each treatment group and these were injected with 500 I.U. of PMS 48 hours after the cessation of nor-ethisterone feeding for the stimulation of their reproductive activity.

** Significant at 5 percent level.

28.6 percent of the ewes from the 50 mg. dose treatment group showed estrus during the first five days of the second and third post-treatment estrus cycles, respectively (18-22 and 35-39 days post-treatment). The control ewes however showed random heats throughout this period.

These observations were similar to those of the first trial. Partial synchronization of estrus after treatment with nor-ethisterone followed by PMS, where effective, was achieved during the first post-treatment estrus cycle. With nor-ethisterone treatment without PMS the estrus synchronization was shown even during the second post-treatment estrus cycle as was in the case of the 40 mg. dose group. The incidence of synchronous estrus with 50 mg. dose (group 5) in the third post-treatment estrus cycle (35-39 days post-treatment) could either be due to the prolonged synchronizing effect of nor-ethisterone or the effect of the drug had disappeared by that time and the ewes came into estrus as in the case of the control ewes and the 30 mg. dosage level (group 1 and 2, table 3).

Since in the second trial there were four ewe lambs in addition to the adult ewes in each treatment group, it would be of interest to examine the effect of nor-ethisterone on estrus synchronization by age groups separately. The adult ewes of the control group randomly exhibited estrus from day 18 to 39 post-treatment but only 25 percent of the control ewe lambs showed estrus during the corresponding period.

(table 4). At 30 mg. daily dose level of nor-ethisterone 33.3 percent of the adult ewes showed estrus from days 35-39 post-treatment; 25 percent of the ewe lambs (PMS treated) from this group came into heat during the first five days post-treatment. This observation substantiates the foregoing statement that progesterone feeding followed by PMS results in synchronization in the first five days.

At the 40 mg. dose level, 50 percent of the adult ewes and 50 percent of the ewe lambs showed estrus during the first five days post-treatment and the remaining 50 percent adult ewes exhibited estrus during the first five days of the second post-treatment estrus cycle (18-22 days post-treatment). The remaining 50 percent of the ewe lambs did not exhibit estrus at all. This indicated that those adult ewes which did not exhibit estrus during the first five days of the first post-treatment estrus cycle were still synchronized as evidenced by their exhibiting estrus during the first five days of the second post-treatment estrus cycle.

At the 50 mg. dosage level, 33.3 percent of the adult ewes showed estrus during the first five days of the second post-treatment estrus cycle (18-22 days post-treatment) and the remaining 66.7 percent of the adult ewes exhibited estrus during the third estrus cycle (35-39 days post-treatment). None of the ewe lambs from this treatment-group exhibited estrus during the entire post-treatment period of 39 days. 25 percent of the ewe lambs from all the three nor-ethisterone

Table 4 - Incidence of post-treatment estrus after nor-ethisterone feeding in adults and ewe lambs (trial II).

Treatment group	Treatment* nor-ethisterone	No. of ewes	% ewes in estrus					
			I cycle (days) 1-5	II cycle (days) 6-17	III cycle (days) 18-22	IV cycle (days) 23-34	V cycle (days) 35-39	
1	Controls							
	Adults	3	0.0	0.0	33.3	33.3	33.3	
	Ewe lambs	4	0.0	0.0	0.0	25.0	0.0	
2	30 mg.							
	Adults	3	0.0	0.0	0.0	0.0	33.3	0.0
	Ewe lambs	4	25.0	0.0	0.0	0.0	0.0	0.0
3	40 mg.							
	Adults	2	50.0	0.0	50.0	0.0	0.0	0.0
	Ewe lambs	4	50.0	0.0	0.0	0.0	0.0	0.0
4	50 mg.							
	Adults	3	0.0	0.0	33.3	0.0	66.7	0.0
	Ewe lambs	4	0.0	0.0	0.0	0.0	0.0	0.0

* All ewe lambs received an injection of 500 I.U. of PMS 48 hours after nor-ethisterone feeding.

treated groups 2, 3 and 4 exhibited estrus during the first five days post-treatment period while none of the remaining treated ewe lambs (75 percent) came into estrus during the entire post-treatment period of 39 days. Syed et al. (1952) have recorded incidence of 30 ewe lambs having been settled at an average age of 256 days and lambed to this breeding. Probably the lower incidence of estrus in the ewe lambs after cessation of progesterone treatment in the present study could be attributed to the residual effect of nor-ethisterone. The small percentage of ewe lambs that showed estrus was perhaps due to the stimulatory effect of PMS. Jochle (unpublished data) reported that nor-ethisterone treatment in maiden ewes delays the onset of puberty which is consistent with the findings of this study.

As no PMS injection was given to the adult ewes in the present trial, the estrus synchronization response appeared to extend to the second and even the third post-treatment estrus cycle. The ewes had missed one or two post-treatment estrus periods which could be explained as silent heats. This observation is in agreement with Hunter (1954) who noted that progesterone treatment appeared to increase the number of silent heats. The incidence of estrus in the control ewes, 30 mg. and 50 mg. treatment groups during the third post-treatment estrus cycle indicated that the ewes exhibited estrus after the inhibitory effect of nor-ethisterone had disappeared. These observations indicated that an injection

of PMS is essential following nor-ethisterone pretreatment for the induction of synchronous estrus in adult ewes even in the normal breeding season. This is inconsistent with the views of Jochle (unpublished data) who indicated that PMS might not be necessary for the adult ewes in their normal breeding season.

Fertility

These data on fertility are reported in table 5. The conception rates in the treatment groups 2-5 receiving 10 mg. and 20 mg. daily dosage of nor-ethisterone with and without PMS injection were 71.4, 50.0, 60.0 and 30.0 percent, respectively. The conception rate in the control ewes under the first trial was 84.6 percent. Differences in conception rates between the control ewes and both the PMS-treated and non-PMS-treated ewes were statistically significant ($P = 0.05$). These observations indicated that even at smaller dosage levels of 10 mg. and 20 mg., nor-ethisterone administration had reduced the conception rate significantly. The supplementation of the treatment with an injection of 500 I.U. of PMS tended to offset the detrimental effect of nor-ethisterone to some extent (table 5). The conception rates obtained in the first trial are lower than those obtained with similar dose levels of provera fed in gelatin capsules, where a conception rate of 70 and 60 percent with 6.6 mg. and 20 mg. dosages respectively was observed (Southcott et al., 1962).

Table 5 - Conception rate in ewes after nor-ethisterone treatment.

Experimental group	Treatment* nor-ethisterone	No. of ewes	No. of ewes bred	No. of ewes lambded	% conception rate
Trial I					
Group 1	Controls	14	13	11	84.6**
Group 2	10 mg. + PMS	12	7	5	71.4
Group 3	20 mg. + PMS	12	10	5	50.0
Group 4	10 mg.	12	10	6	60.0
Group 5	20 mg.	12	10	3	30.0
Trial II					
Group 1	Controls				
	Adults	3	3	2	66.7
	Ewe lambs	4	1	0	0.0
Group 2	30 mg.				
	Adults	3	2	1	50.0
	Ewe lambs	4	1	0	0.0
Group 3	40 mg.				
	Adults	2	2	1	50.0
	Ewe lambs	4	2	0	0.0
Group 4	50 mg.				
	Adults	3	3	3	100.0
	Ewe lambs	4	0	0	0.0

* All ewe lambs in trial II were injected with 500 I.U. of PMS each 48 hours following nor-ethisterone treatment.

** Significantly different from the other treatment groups at 5 percent level.

In the second trial conception rates with dosage levels of 30 mg., 40 mg. and 50 mg. of nor-ethisterone in adult ewes were 50, 50 and 100 percent respectively as compared to 66.7 percent in the control adult ewes. Since 66.7 percent of the adult ewes in the treatment group receiving 50 mg. of nor-ethisterone were bred during the third post-treatment estrus cycle (table 4) when the effect of nor-ethisterone had probably disappeared, a higher conception rate (100 percent) in this treatment-group can be explained. Contrary to these findings Evans et al. (1962) and several other workers have found no apparent effect of the progestational treatment on the fertility of the treated ewes. It seems that the effect of nor-ethisterone feeding on fertility is more pronounced than other progestational compounds. This is probably due to the comparatively stronger action of this drug. White et al. (1959) indicated that nor-ethisterone when administered orally is eight times more potent than injections of crystalline progesterone. The present observations agreed with the findings of Hogue et al. (1962) who observed somewhat lower fertility in ewes synchronized with provera than with those bred from normal estrus.

In the present study none of the four bred ewe lambs conceived. Although Spencer et al. (1942) observed that about 70 percent of the ewe lambs bred conceived consistently from year-to-year. The failure of all the bred ewe lambs to become pregnant in the present study indicates a possible detrimental

effect of nor-ethisterone administration on the conception of these ewe lambs.

Twinning

Although 30.8 percent multiple births had been recorded in the farm flock during the spring season of 1963, there were no multiple births among the experimental ewes. A slight decrease in the twinning rate in progesterone treated ewes has been reported by Botkin et al. (1963). On the contrary Robinson (1956) recorded an appreciably increased twinning rate in progesterone-PMS treated ewes but this increase was not statistically significant. In the present two trials 23 out of 37 ewes had lambed after an average lambing interval of 8-9 months. Ten of the ewes lambing in trial I had given twin lambs during the previous lambing season of the same year. In addition to the possible detrimental effect of nor-ethisterone on the twinning percentage, the breeding of the ewes very early or late in the breeding season or a shorter lambing interval may have adversely affected the twinning rate reducing it to zero during the two trials. However, the ewes lambing in the second trial had an entire year between their two lambings, yet these gave no twin births. Therefore it appears that the nor-ethisterone treatment did have some detrimental effect on the twinning percentage.

Gestation

The average length of gestation in the control ewes was 152.6 days while in the nor-ethisterone treated ewes it was 154.1 days. Nor-ethisterone treatment seemed to prolong the gestation period (an average of 1.5 days longer than that of the non-treated ewes). Before confirming this observation, a larger number of sheep should be studied.

False Estrus

During both of the trials, 6 ewes (2 from the control ewes and 4 from the nor-ethisterone treated ewes) showed two heat periods following cessation of hormonal treatment but lambed from breeding during the first estrus. These observations are substantiated by the findings of Addleman et al. (1963a) who observed similar false heats in hormone treated ewes indicating a slight upset in the hormonal balance from progesterone administration. Williams et al. (1956) observed estrus during pregnancy in 5 Western ewes (22 percent) and in 15 Rambouillet ewes (62 percent). Two pregnant control ewes showed estrus in the present trials while the same phenomenon was manifested in 4 of the treated ewes. It is possible that incidence of estrus in pregnant ewes of the Awasi breed may not be an uncommon feature since two of the six ewes exhibiting estrus during pregnancy had received no progestational treatment.

Birth Weights

The data of the present study indicated that nor-ethisterone treatment had no effect on the birth weights of the lambs born to the treated ewe.

The birth weights of male and female lambs from the treated ewes and the untreated control ewes of both trials are given in table 6.

Table 6 - Birth weights of lambs in trial 1 and trial 2.

Treatment	Average birth weights				
	Male		Female		Average
	No.	Lbs.	No.	Lbs.	Lbs.
Nor-ethisterone	9	10.1	15	8.0	8.8
Controls	6	10.5	7	8.1	9.2

SUMMARY AND CONCLUSIONS

1. Two experiments were conducted on 89 fat tailed Awasi ewes which included adult ewes and ewe lambs. Nor-ethisterone in daily doses of 10, 20, 30, 40 and 50 mg. for each ewe for 12 days, with or without 500 I.U. of PMS, was administered orally to different groups.

2. Dosage levels of 40 mg. and 50 mg. of nor-ethisterone were completely adequate for inhibiting estrus during treatment while lower levels of 10, 20 and 30 mg. were ineffective in completely suppressing estrus.

3. Synchronizing effect of nor-ethisterone with 10, 20 and 30 mg. daily dosage levels was poor while 50 mg. appeared to be an over dose in that estrus was inhibited for two post-treatment estrus cycles.

4. Synchronization of estrus was obtained in 100 percent of the adult ewes fed 40 mg. of nor-ethisterone without an injection of PMS but the estrus was exhibited during the first five days of the first and second post-treatment estrus cycles (days 1-5 and 18-22 post-treatment).

5. Only 50 percent of the ewe lambs receiving a treatment of 40 mg. nor-ethisterone followed 48 hours later by an injection of 500 I.U. of PMS exhibited synchronous estrus.

6. It appears that in order to obtain synchronous estrus in adult cycling ewes after a pretreatment with nor-ethisterone an injection of PMS is essential to reduce its

residual effect.

7. Nor-ethisterone treatment seems to have a detrimental effect on conception rate. An injection of PMS appeared to partially restore the incidence of conception.

8. In ewe lambs, puberty appeared to be retarded in that 75 percent did not show any estrus after a pretreatment with nor-ethisterone although it was followed 48 hours later by an injection of 500 I.U. of PMS.

9. Twinning rate appears to have been influenced adversely by nor-ethisterone treatment.

10. The results of this study indicate that nor-ethisterone in adequate amounts has the ability to stop ovulation thus enabling synchronization of estrus within first five days post-treatment, if the progestational treatment is followed by an injection of PMS. If necessary this treatment could be used to induce ovulation in anestrous ewes thus enabling the production of three lamb crops in two years.

11. The depressant influence of nor-ethisterone on fertility may render the drug of limited use in a sheep breeding program.

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A P P E N D I X

Problems for Further Research

The present study has answered many of the questions that inspired the initiation of this work on the synchronization of estrus by the use of nor-ethisterone and PMS. But as in all studies many new problems arose and remained unsolved. Therefore the author of this thesis recommends that further work be executed so that some of the answers can be found for these unsolved problems. The questions relative to this study that require further work are as follows:

1. What is the optimum dose of nor-ethisterone and PMS that will most effectively synchronize estrus in sheep?
2. Does nor-ethisterone interfere with the fertilization and nidation of the ovum? If so, by what mechanism?
3. To what extent does nor-ethisterone treatment influence twinning rate?
4. Is there any extended residual effect of nor-ethisterone? If so, what are the physiological reasons for such an effect?
5. Does nor-ethisterone retard puberty in maiden ewes and what is the hormonal relationship that causes this retardation?