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PROGRESS WITH THE CONTROL OF OESTRUS AND OVULATION IN FARM LIVESTOCK

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The process of reproduction in the female mammal involves a complex series of inter-related events which must take their place in an orderly fashion before conception can occur. This sequence of events is dependent on endocrine activity originating from four different regions of the body, viz.:

(1) the hypothalamus (producing gonadotrophin releasing and inhibiting factors)
(2) the anterior pituitary gland (producing the gonadotrophins luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin)
(3) the ovary (producing the gonadal steroid hormones)
(4) the uterus (producing a luteolytic factor which is probably the prostaglandin $PGF_{2\alpha}$)

In pregnant and cycling animals the production of any of these endocrine components at a specific time depends on the presence or absence of one or more of the other components.

A deficiency in any one of the components usually leads to infertility and it is only recently, with the advent of sensitive and specific methods of measuring the level of protein and steroid hormones in peripheral plasma, that an understanding of some of the types of infertility in farm species has been possible.

Under normal situations the cow shows little or no seasonal variation in fertility, whereas most breeds of sheep show a period of seasonal anoestrus which limits their annual productivity. Most breeds of both species as well as pigs have a lactation anoestrus during which the ovaries are inactive the uterus regresses and undergoes repair in preparation for the next pregnancy. In British breeds of sheep those animals which lamb after the mid-point of the breeding season have a *post-partum* anoestrus confounced with seasonal anoestrus, although it must be stressed that these two periods are separate entities.

New information available concerning the endocrine changes responsible for the initiation of oestrus and ovulation is discussed in this paper in order that the difficulties involved in developing practical methods of controlling oestrus and ovulation may be more fully appreciated.

The Pituitary Gland and its Control.

Most workers are agreed that the release of LH is at basal levels during most of the bovine and ovine oestrous cycles. It is also generally agreed that there is a high release of LH at approximately the onset of oestrus in the cow and 6-8 h after onset in the ewe, the level of LH in the blood at this time rising to 50-100 times that found during the rest of the cycle. These elevated levels last 8-10 hours; the rise sharp and the fall equally dramatic. Some workers (Schams & Karg, 1969; Henricks, Dickey & Niswender, 1970; Snook, Saatman & Hansel, 1971) have also detected increased LH levels in the blood of cows and heifers on about Day 8 or 9 of the oestrous cycle (that is 8 or 9 days from the beginning of the previous oestrus), although the concentration of LH does not rise as high. Schams & Karg (1969) and Snook *et al.* (1971) also detected a smaller increase in the level of LH in the blood of some of their animals 4-7 days before the next oestrus. Work by my colleagues has indicated that mid-cycle LH peaks also occur in some instances in the ewe (Foster & Crighton, unpulished data).

The high release of LH at the time of oestrus is thought to be the triggering mechanism for ovulation and this has been shown to be the case in many species. If the effect of gonadotrophin is prevented in some way (for example LH antiserum into the animal) ovulation may be prevented. On the other hand, if LH is injected at times when the LH peak does not normally occur, then ovulation can result provided a suitable pollicle is present in the ovaries. This knowledge is used as a basis for administering LH in the form of human chorionic gonadotrophin (HCG) to induce ovulation in cows and pigs with ripe follicles which fail to ovulate.

The reason for elevated levels of LH at other times in the cycle is less certain and Snook *et al.* (1971) correlated their occurrence with the growth of follicles which subsequently regress without ovulation. It is known these follicles grow and regress throughout the cycle but more so at specific periods. Following ovulation a corpus luteum is usually formed within the structure of the ripe follicle and this becomes an endocrine gland which secretes the hormone progesterone. It is thought that in the cow and ewe LH, possibly in conjunction with prolactin, is also required for the growth and maintenance of the corpus luteum.

The pattern of FSH release has not been studied so extensively due to the greater difficulties of developing a suitable radio-immunological assay for measuring blood levels of this hormone. Recently however Karg (1972) has presented information concerning the release of FSH in the cow where increased release occurred simultaneously with the increased LH release; that is just after the onset of oestrus. L'Hermite, Niswender, Reichert & Midgley (1972) have shown that there is an FSH peak coincident with the LH peak 6-8 hours after the onset of oestrus in the ewe. This conflicts with previous theories which assumed that FSH was released earlier than LH and was concerned with the rapid preovulatory growth of the follicle which takes in the last few hours before ovulation. However, Laster (1972) has shown that follicular growth is increased in heifers injected with FSH and its effect is increased if a small amount of LH is also injected. Thus is still seems likely that in the cow, both LH and FSH are involved in controlling growth of the follicles. Similar experiments indicate that this is also the case in the ewe.

Recent evidence indicates that prolactin may also be concerned with control of the oestrous cycle. An increase in prolactin release has been shown to occur at about the same time as the LH and FSH peaks 6-8 hours after the onset of oestrus in the ewe (Cumming, Brown, Goding, Bryant & Greenwood, 1972). It has also been shown that prolactin along with LH may be necessary for the maintenance of the corpus luteum in the ewe (Denamur, Martinet & Short, 1973)

Hormone release from the anterior pituitary is controlled by low molecular weight materials produced in the hypothalamus and particularly from the median eminence region, which pass down a series of portal vessels into the anterior pituitary where they either stimulate or inhibit release of the various hormones secreted by this gland. These substances are termed 'releasing' or 'inhibiting' factors according to the action they exert on the release of hormones from the pituitary gland.

Hypothalamic extracts when incubated with the pituitary of many species have been shown to cause LH and FSH release. For example Wilks & Hansel (1971) showed that such extracts caused LH release from the pituitary of cattle. On the basis of these and similar experiments it has been thought for many years that there were two releasing factors involved in the release of LH and FSH, termed 'LH-releasing factor' (LH-RF) and 'FSH-releasing factor' (FSH-RF). However, it has recently been postulated by Schally, Arimura, Baba, Nair, Matsuo, Redding, Debeljuk & White (1971) and by Matsuo, Baba, Nair, Arimura & Schally (1971) that LH-RF and FSH-RF are in fact one substance which will release both LH and FSH. They have isolated and purified a single substance from the pig hypothalamus which causes release of both LH and FSH from the pituitary of several species. Schally's group has determined the structure of this molecule and synthesised it. This molecule has a decapeptide structure with an amino acid sequence as follows:

(Pyro) Glu-His-Try-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

The effects of synthetic preparations of this releasing factor on pituitary gonadotrophin release have been tested in several species. It will cause both LH and FSH release from the ovine pituitary *in vitro* (Crighton & Foster, 1972). It will also cause LH release and ovulation when injected into ewes, both during the breeding season and during the seasonal and lactational anoestrous periods (Reeves, Arimura, Schally, Kragt, Beck & Casay, 1972; Foster & Crighton, 1972). Thus there seems to be a single substance found in the hypothalamus which is capable of causing both LH and FSH release. Whether this single molecule is the naturally-occurring releasing factor for LH and FSH remains to be finally proved.

The control which the hypothalamus exerts over the pituitary is influenced by several factors including the blood level of the ovarian hormones oestrogen and progesterone. Oestrogen is secreted by cells in the Graafian follicles, and in sheep and cattle the level of oestrogen in the blood begins to increase 1-2 days before oestrus during the period of high follicular growth (Wetterman, Hafs, Edgerton & Swanson, 1972). This gives a peak of oestrogen in the blood just prior to the ovulatory peak of LH. Injection of oestrogen into ovariectomised cows causes a high release of LH about 10 hours later (Cummins, Blockley, Brown & Goding, 1972). Similarly, Radford, Wallace & Wheatley (1971) showed that injection of oestrogen into anoestrous ewes caused a massive release of LH within 24 hours. Thus it is thought that the increased oestrogen level in the blood just before oestrus is probably the triggering mechanism for LH release and this effect is probably exerted via the hypothalamus.

In normal cows and ewes the corpus luteum, which is formed after ovulation, secretes large amounts of progesterone, and as a consequence the level of progesterone in blood rises as the corpus luteum develops during the first few days after ovulation. Progesterone has been shown to inhibit gonadotrophin release from the pituitary and so, when the progesterone level is high, there is a low release rate of gonadotrophin from the pituitary gland. When the corpus luteum begins to regress 3-4 days before the next oestrus the blood level of progesterone also falls until, just prior to the time of the next oestrus, its concentration in the blood is negligible. The fall in the progesterone level of blood is possibly a factor in the triggering mechanism of LH release and also possibly of FSH release. The hormone changes thought to occur in relation to the bovine oestrous cycle are presented diagrammatically in Figure 1.

LH and FSH may themselves act on the hypothalamus to decrease release of releasing factor(s). This negative feedback system operates in such a way that as the LH or FSH level in the blood increases, so the stimulus for their release is decreased.

Ovarian Function

Follicular growth.

More information is available on follicle growth in sheep than in cattle, but the same pattern of growth probably takes place in both species. A biphasic pattern of growth in the bovine was suggested from the data of Hammond (1927), the first phase of growth of the follicle occurring over the period Days 3-8 of the cycle, and the second occurring just prior to ovulation. This was later confirmed by Rojakoski (1960) and is similar to that described for the ewe by Hutchinson & Robertson (1966). The major problem with this type of study is following the growth of individual follicles throughout the cycle which involves repeated observations in the same animal.

The marking of individual follicles with Indian ink has shown that the growth of the follicle for ovulation is very rapid in the cow (Dufour, Whitmore, Ginther & Casida, 1972). Only when the largest follicle was marked on or after day 18 of the cycle was this the one ovulated. Based on similar results from the sheep Smeaton & Robertson (1971) postulated that there may be 4 waves of follicle growth each lasting for about 4 days, each batch of follicles developing and then regressing to be replaced by new ones. Only follicles developing in the last 4-days phase of growth being fully developed and ovulated at oestrus. The mechanisms behind these repeated phases of follicle growth are not understood, but the possibility remains that there

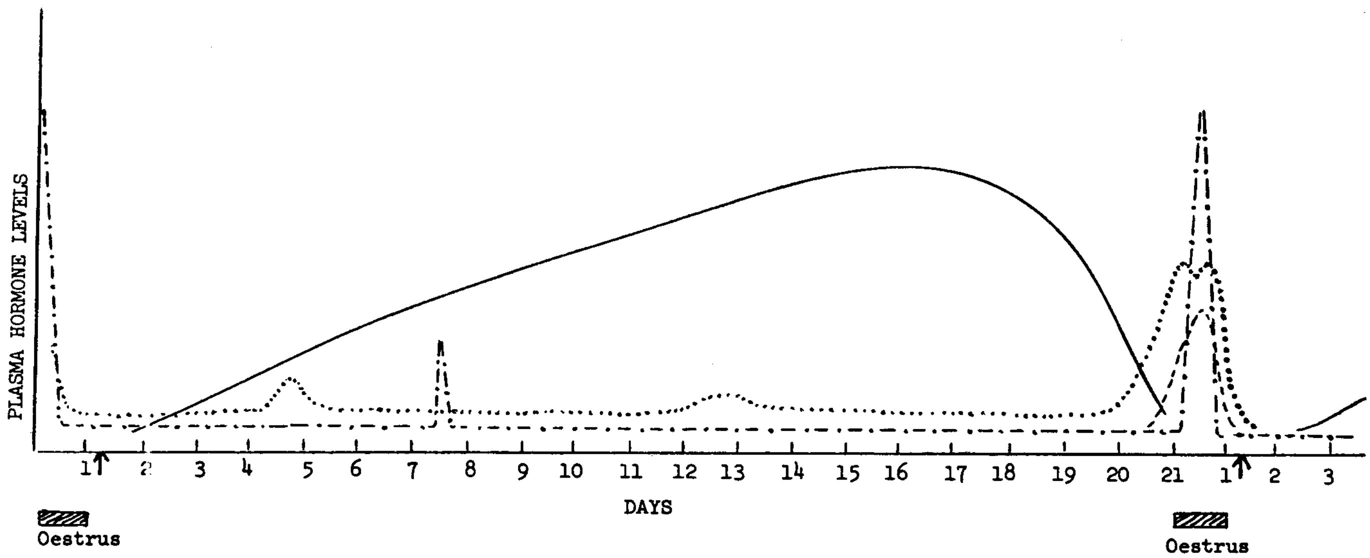


Fig. 1 *Diagrammatic representation of the concentrations of gonadotrophins and ovarian steroids in the blood during the bovine oestrous cycle.*

The level of progesterone (———) increases and decreases as the corpus luteum grows and then regresses. The falling progesterone level at the end of the cycle is probably one of the causal factors for FSH release (-------). Release of FSH, together with the small amount of LH released at this time, causes follicle growth. As follicles grow there is an increase in the release of oestrogen (. . . . . .). The rising oestrogen level is probably a triggering mechanism for the LH peak (- - - - -) which follows. Oestrogen is also responsible for behavioural oestrus. The LH peak observed at the onset of oestrus causes ovulation 20-26 hours later.

may be some physiological mechanisms which require such growth, and these may be endocrine in nature. The results also suggest that the final growth of a potential follicle for ovulation is a very rapid process and this fact is illustrated by the work of Laing (1965) who demonstrated that surgical suppression of an active corpus luteum resulted in oestrus approximately 4 days later.

Levels of steroid hormones during the oestrous cycle.

The production of the steroid hormones, progesterone and oestrogen, is very important in controlling the periodicity of the oestrous cycle in non-pregnant animals, the preparation of the uterus for implantation and the maintenance of the pregnancy.

Plasma progesterone levels are low at oestrus in both cattle and sheep, begin to rise slowly around day 3-4 of the cycle, reaching a peak and plateauing mid-cycle, falling very rapidly about 2 days before oestrus and remaining low throughout oestrus (Shemesh, Lindner & Ayalon, 1971; Swanson & Hafs, 1971; Thorburn, Basset & Smith, 1969; Basset, Oxborrow, Smith & Thorburn, 1969).

Plasma oestrogen levels show a peak just before the onset of oestrus in both the cow and the ewe (Christensen, Wiltbank & Hopwood, 1971; Shemesh, Ayalon & Lindner, 1972; Cox, Mattner, Shutt & Thorburn, 1971; Cox, Mattner & Thorburn, 1971; Mattner & Braden, 1972). This peak precedes the LH peak and in the sheep is thought to stimulate the pattern of LH release typical at oestrus. Mid-cycle peaks have been recorded in peripheral plasma of the cow (Christensen *et al.*, 1971; Pope and co-workers, unpublished) the significance of which is obscure but it may be useful for uterine receptivity of the embryo or transport of the fertilised ovum along the tract. Similar mid-cycle release of oestrogen has been shown in ovine peripheral plasma (Cox *et al.*, 1971) but by measuring ovarian vein levels, Mattner & Braden (1972) were able to show 3 mid-cycle peaks on days 3-4, 6-9 and 11-15. These may well be a result of the phases of follicle growth proposed by Smeaton & Robertson (1971).

Hormonal control of oestrus.

The two ovarian steroid hormones (progesterone and oestrogen) have been shown to induce oestrus in spayed heifers (Cornick & Shelton, 1969) and sheep (Robinson, 1954; Scaramuzzi, Tilison, Thorneycroft & Caldwell, 1971). However, the mechanisms involved appear to be slightly different. Robinson (1954) demonstrated that high doses (5 mg) of oestradiol dibenzoate (ODB) would induce oestrus when given as a single intramuscular injection. When repeated this treatment produced a refractory condition which could be alleviated by progesterone administration. The dose of ODB required to induce oestrus was decreased from 5 mg to 20 μg when progesterone pretreatment was practised, illustrating the need for an active corpus luteum before overt oestrus could be shown in the ewe.

In contrast, Cornick & Shelton (1969) demonstrated that low levels of ODB (100 μg) could induce oestrus in spayed heifers, and this treatment could be repeated with no loss of sensitivity. However, large doses of ODB had an inhibitory effect on subsequent injections of ODB, and this condition could only be overcome with the use of progesterone.

It is well known that sheep experience a 'silent heat' at the onset of the breeding season before they are able to show behavioural oestrus. In *post-partum* cows this phenomenon also occurs (Pope, Gupta & Munroe, 1969), and these silent heats, or at least the progesterone from the resulting corpus luteum, may be necessary to sensitise the hypothalamic hypophyseal system from a refractory state arising from continued high levels of oestrogen produced during late pregnancy. Support for this theory arises from data showing that nulliparous heifers do not usually show 'silent' heats before they commence to show oestrus.

The maintenance of pregnancy.

During pregnancy the progesterone level, instead of falling after the luteal phase of the oestrous cycle, is maintained until just before parturition in both the ewe and the cow. The presence of the conceptus does not therefore appear to have any effect until day 18 of pregnancy in the cow and day 14 in the sheep. The maintained levels are due to the continued activity of a functional corpus luteum instead of its normal regression (Schams, Hoffman, Fischer, Marz & Karg, 1972; Basset *et al.*, 1969). Comparison of jugular and ovarian venous levels (Thorburn & Mattner, 1971) show that the progesterone level is associated with the metabolic clearance rate of the hormone from the body, as well as with the continued corpus luteum activity.

Why does the progesterone level fall if the animal is not pregnant? Hysterectomy studies have been shown to increase the life span of the corpus luteum (Anderson, Neal & Melampy, 1962; Moor & Rowson, 1964). Because of cost more work has been completed in sheep than in cattle, but the available information for both species does indicate that a local utero-ovarian relationship is involved.

Hysterectomy as late as day 15 of a 17-day sheep cycle will maintain the functionality of the corpus luteum, providing degenerative changes have not already been initiated. Unilateral hysterectomy has the same effect if the corpus luteum is in the ipsilateral ovary, but not in the contralateral ovary (Inskeep & Butcher, 1966). Evidence for this local relationship being endocrine has been established by Caldwell & Moor (1971) who collected uterine vein plasma from ewes on days 8 and 14 of the cycle and jugular venous plasma on day 14 of the cycle, and infused these samples into the ovarian artery of an ovary with a functional corpus luteum on day 8 of the cycle. Day 8 uterine vein plasma and day 14 jugular venous plasma had little effect on progesterone levels in the ovarian vein or cycle length, but uterine vein plasma collected on day 14 caused the progesterone levels to fall markedly and oestrus to be initiated on day 10-11 of the cycle instead of the normal control 15-17 days.

Since these studies much information has accrued suggesting that the active substance is a prostaglandin $PGF_{2\alpha}$. Evidence for this has been presented for both cattle and sheep, and changes in the endometrial content during the oestrous cycle of this prostaglandin have been reported (Wilson, Cenedella, Butcher & Inskeep, 1972; Harrison, Heap, Horton & Poyser, 1972). Infusion of $PGF_{2\alpha}$ has also been shown to cause luteal regression (Barrett, De Blockley, Brown, Cumming, Goding, Mole & Obst, 1971; Restall, Hearnshow, Gleeson & Thorburn, 1973) although the precise mechanism of action is not yet clear.

These basic studies of the endocrine control of oestrus and ovulation are of vital importance in appreciating the control methods that have been used albeit somewhat unsuccessfully in the past and the potential of more modern developments for the successful synchronisation of oestrus and out-of-season breeding, both of which will be discussed in the following section.

Synchronization of Oestrus and Ovulation.

The successful synchronization of oestrus in farm animals has several practical advantages and the general lack of success of methods previously employed have not decreased the enthusiasm of endocrinologists who wish to control the reproductive cycles of female mammals. The detection of oestrus is a limiting factor in the utilisation of artificial insemination, especially where animals are kept under range conditions. Synchronization of ovulation and oestrus would enable large numbers of animals to be inseminated following a chronological schedule, if possible without the necessity of detecting oestrus. Synchronization has particular application in the breeding of beef cows and heifers to ensure a short calving period at a pre-determined season and in sheep to permit the use of artificial insemination and batch lambin while in pigs the technique would permit batch farrowing. The application to the dairy cow is not so obvious although it is still applicable to the breeding of heifers. Many of the experiments carried out so far have also aimed at improving fertility as well as synchronization, for low conception rates are often a problem under conditions of large scale animal production.

During the 1960s synthetic analogues of progesterone were developed and hopefully screened as synchronizing agents; the work of this period is reviewed by Lamond (1964), Robinson (1967), Hansel (1967), Hunter (1968), Wiltbank (1970) and Cullen (1971). It is therefore necessary here only to review recent evidence in this field. Despite the wide range of progestagens available (some of which are listed below), a period of transitory infertility following progestagens withdrawal has been widely observed. Progestagens used in recent synchronization experiments:

FGA

17αacetoxy-9α-fluoro-11βhydroxy-4-ene-3,20-dione – Synchronmate. (Robinson, 1967, 1970a, 1970b, in sheep)

MAP

6-α-methyl-17-α-acetoxyprogesterone (Zimbelman, 1963, in cattle; Rahman & Kitts, 1967, in sheep; Glimp, Deweese & Dutt, 1968, in sheep)

CAP

6-chloro-Δ^6-17-acetoxyprogesterone (Wagner, Veenhuizen, Gregory & Tonkinson, 1968, in cattle; Rahman & Kitts, 1967, in sheep)

DHAP

Dihydroxy progesterone acetophenide (Wiltbank, Shumway, Parker & Zimmerman, 1967, in cattle; Brown, Peterson & Foote, 1972, in cattle)

MGA

Melengestrol acetate (Boyd & Tasker, 1971, in cattle)

17-α-ethyl-19-nortestosterone

17-α-ethinyl-19-nortestosterone (Liang & Fosgate, 1971, in cattle: Smith & Vincent, 1973, in cattle)

Many of the synthetic progestagens have the advantage that they can be administered orally, thus eliminating the need to handle animals individually. This means that a wide tolerance in dose rate is necessary and withdrawal of the progestagen from the system is not very precise. Recently other methods of administration have been investigated. Subcutaneous implants of 17-α-ethyl-19-nortestosterone were used in combination with oestradiol valerate injections. There is a continuous slow release of progestagen from such implants followed by a sharp end point on removal. Again fertility was depressed at the post-treatment oestrus (Wiltbank, Sturges, Wideman, Le Fever & Faulkner, 1971). In cattle and sheep the use of progestagen-impregnated vaginal pessaries has also been investigated as a method of administration and although in sheep the uptake of progestagen is effective in inhibiting ovulation, and a sharp end point on removal results in oestrous synchronization, fertility is usually depressed (Robinson, 1967).

In cattle the retention of pessaries is poor especially in multiparous cows (Scanlon, Neville, Burgess & Macpherson, 1971; Short, 1971). The problems arising from the use of these materials have been possibly related to a general lack of information concerning the pattern of gonadal steroids during the normal bovine, ovine and porcine oestrous cycle, and it is only recently that sensitive techniques have been developed for monitoring the steroid hormonal levels concerned with controlling the reproductive system, and investigations carried out concerning the causes of infertility following treatment with progesterone. A greater understanding of the physiological effects of progestational agents is undoubtedly required before successful synchronization can be achieved with these compounds.

Treatment with the progestagen MGA resulted in depressed follicular development in cattle (Zimbelman, 1966; Guthrie, Lamond, Henricks & Dickey, 1970; Hill, Lamond, Henricks, Dickey & Niswender, 1971; Lamond, Dickey, Henricks, Hill & Leland, 1971). Fewer follicles over 3 mm diameter were present and the majority of smaller follicles were atretic. Britt & Ulberg (1972) noted elevated levels of progesterone in peripheral blood following synchronization with MGA. In the untreated animals the blood levels of progesterone fell from 4,2 to 0,5 ng/ml during the last three days of the cycle. Following progestagen treatment the levels fell from 6,8 to 3,1 ng/ml during the three days prior to oestrus. In the following post-treatment cycle the levels were again normal Henricks, Hill & Dickey (1970) recorded a higher incidence of fertilisation failure and retardation of cleavage in heifers which had an average progesterone concentration of more than 2,8 ng/ml during the four days before oestrus. Serum concentrations of luteinising hormone were also elevated in heifers receiving progestagen treatment (Hill *et al.*, 1971).

The uterus also shows evidence of a hormonal imbalance following progestagen (MGA) treatment. The endometrial and glandular cell heights were higher after progestagen therapy than in the controls (Wordinger, Dickey & Hill, 1970) and these authors found plasma progesterone levels to be similar in treated and control animals and they suggested that the cytological difference was due to diminished oestrogen influence in the treated animals. Lauderdale & Ericsson (1970) investigated the physiology of sperm in the uterus of progestagen (MGA) treated cattle. Bull sperm labelled with tetracycline hydrochloride was used to determine physiological change as indicated by persistence or absence of the label following exposure for five hours to the uteri of cattle The greatest label removal occurred at the post-treatment oestrus following progestagen treatment which the authors assumed indicated a uterine environment less favourable to sperm survival Failure of fertilisation following treatment with CAP was also demonstrated by Wagner *et al.* (1968). Cervical mucus was also found to be abnormal following progestagen therapy (Hohnson & Ulberg, 1965; Hill *et al.*, 1971; Boyd, Gibbons & Tasker, 1972).

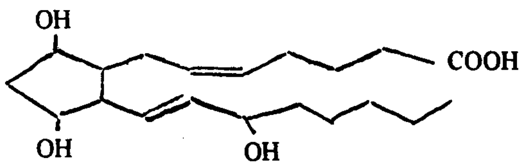
Fertilisation in sheep was greatly reduced following synchronization with vaginal sponges impregnated with fluorogestone acetate, although it was normal following synchronisation by progesterone injection. An excess of cervical mucus was implicated in the impairment of sperm transport (Moore, Quinlivan, Robinson & Smith, 1967). More recently Robinson and his co-workers have been examining the influence of oestrogen and progesterone on the cervix and sperm transport. Although adequate progesterone priming was required in spayed ewes, oestrogen levels were critical to sperm transport and the maintenance of a cervical population (Allinson & Robinson, 1972).

Thus there is evidence of a disturbed balance of hormones following synchronizing treatments and that this should result in infertility is not surprising. The work of Rowson, Lawson, Moor & Baker (1972) indicated that very precise synchronization is required between the embryo and uterus. Appreciable loss of embryos occurred in cattle when the synchronization of donors and recipients for embryo transfer was displaced as little as 24 hours. This synchronization is far more precise than that required in the sheep. The authors suggested that under certain conditions of management asynchrony may exist between the embryo and the uterus which could cause an appreciable fall in conception rate.

Therefore although synchronization in cattle and sheep following progestagen treatment is well documented the fertility at the post-treatment oestrus is generally poor and a greater understanding of the basic physiology is necessary before methods can be improved to give more precise synchronization and better fertility with progestagens.

Recent findings on the use of prostaglandins.

In sharp contrast to the widescale failure of progestagens to gain acceptance for oestrous cycle control comes the remarkable discovery that selected members of compounds collectively known as the prostaglandins are successful in controlling both oestrus and ovulation in cattle. The prostaglandins were discovered in the 1930s when scientists in Britain, Sweden and the United States became aware that substances contained in seminal plasma had a range of biological effects in mammals. Von Euler of Sweden eventually deduced that these substances are fatty acids. (For reference concerning chemical nature and biological activity of these compounds see Pike, 1971). The particular analogue most widely used in various aspects of reproductive physiology is Prostaglandin F2α (abbreviated $PGF_{2\alpha}$) for which the chemical configuration is given here.



Prostaglandin $PGF_{2\alpha}$

The name prostaglandins originated because the earlier investigators thought that the active material found in sheep semen originated from the prostate gland whereas they are in fact, produced by the seminal vesicles in this species. Prostaglandins are widely distributed in mammalian tissues and body fluids and the coral *Plexaura Homomalla* found in reefs off the Florida Coast surprisingly contains high concentrations of a prostaglandin precursor which can be converted into biologically important prostaglandins (c.f Pike, 1971). In current ecperimental work the synthesised molecule is usually used and the use of prostaglandins in human reproduction has been reviewed by Beazley (1971) and Karim (1971, 1972).

The possibility that $PGF_{2\alpha}$ is the luteolytic factor produced by the mammalian uterus which then causes corpus luteum regression in the ipsilateral ovary has been reviewed earlier. Since the maintenance of the level of progesterone from the corpus luteum is a key factor in oestrous cycle control then it seemed logical that experiments were required to study the effect of $PGF_{2\alpha}$ on oestrous cycle control in cattle.

In England the early experiments have been carried out at Cambridge by L.E.A. Rowson and his colleagues to whom I am indebted for supplying details In order to simulate the natural situation, Rowson's first experiments have concerned the administration by non-surgical means of $PGF_{2\alpha}$ directly into the uterine horn ipsilateral to the ovary containing the corpus luteum. This procedure caused lutoelysis and was followed by oestrus in a large percentage of heifers provided the treatment was given after the fourth day of the cycle (Rowson, Tervit & Brand, 1972a).

A total of 78 heifers was used to test the efficacy of various dose levels and treatments at various stages of the cycle. The injection of 0,5 milligrams in 1 ml phosphate buffer via an inseminating pipette was partially successful when given between days 5 to 16 of the cycle, oestrus occurring three days after treatment. Doubling the dose was also partially successful but more promise was shown by giving 0,5 milligrams/day for two consecutive days as the following table shows:

Table 1

Effect of a double injection of 0,5 mg prostaglandin $PGF_{2\alpha}$

Stage of Cycle (Days)	Animals (No.)	Animals showing oestrus (No.)	Interval from start of treatment to oestrus (days)	No effect (No.)
1-4	6	0		6
5-9	9	8	(3;3;3;3;3;3;3;3)	1
10-14	6	6	(3;3;3;3;3½;3½)	0
15-16	6	6	(2;2;3;2;3;3)	0

(Taken from Rowson, Tervit & Brand, 1972b)

Of 28 animals given 1 ml phosphate buffer by the same route on two consecutive days none showed modification of the oestrous cycle.

In a further experiment PMSG was given mid-cycle followed by two daily doses of 0,5 milligrams $PGF_{2\alpha}$. Forty eight eggs were recovered from five donors of which 37 were fertilized (almost all the unfertilized eggs came from one animal, the remaining four giving 26 fertilized eggs from 29 ovulations). Three out of four recipient cows, synchronised with $PGF_{2\alpha}$ which recieved eggs from donors also synchronised became pregnant.

It is likely that a considerable volume of experimental work will be carried out on the use of $PGF_{2\alpha}$ for synchronizing the oestrous cycle of cattle, sheep and other mammals. Certainly this is the most exciting development which has occurred recently in this most difficult area of oestrous cycle control.

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