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# MECHANISMS CONTROLLING THE FORMATION AND PERSISTENCE OF THE CORPUS LUTEUM<sup>1</sup>

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Mechanisms which control formation of corpora lutea during the estrous cycle, and particularly factors affecting their persistence and regression in various reproductive stages, have been of considerable interest to physiologists concerned with developing methods for control of the estrous cycle in domestic animals. Some recent reviews on control of ovarian function are those by Chester Jones and Ball (30), Anderson *et al.* (9) and Short (121).

## Morphologic Aspects

The mammalian ovary has two principal functions: the production and release of ova and the synthesis and secretion of hormones which regulate the reproductive tract and secondary sexual characteristics. These hormones also influence mating behavior and affect metabolism. Following ovulation, the wall of the ruptured follicle undergoes structural and functional changes which transform it into a transient endocrine gland known as the corpus luteum. While the early development of the corpus luteum appears to be quite similar in many mammalian species, the functional life span varies according to whether the animal is nonpregnant, pseudopregnant, pregnant or lactating. In eutherian mammals, it is generally accepted that the granulosa cells are transformed into luteal cells of the corpus luteum. The fate of theca interna cells is less clear and there appear to be species differences as to their subsequent functional significance in the corpus luteum. The literature pertaining to the histogenesis of the corpus luteum has been reviewed by Marshall (79); Corner (31, 32); Hett (60); Pratt (103); Harrison (58, 59) and Brambell (23). According to Amoroso and Finn (2) the original description of the corpus luteum is usually credited to Volcherus Coiter in 1573, but Harrison (58) has stated that Vesalius had observed it in the human ovary about 30 years earlier.

The developmental morphology of the corpus luteum in the ewe has been described by Marshall (78), Grant (50), Quinlan and Mare (105), Casida and McKenzie (28) and Warbritton (128); in the goat by Harrison (57); in the sow by Corner (31, 32, 34, 35) and Barker

(19); in the cow by McNutt (73, 74), Hammond (52), Höfliger (62) and Asdell *et al.* (17); and in the mare by Harrison (56). The mature bovine corpus luteum may show a fluid-filled cavity, whereas this gland is a solid structure in the ewe, goat and sow. According to Harrison (59), it has been observed in several species that theca interna cells invade the granulosa between day 1 and day 3 and that vascularization of the gland occurs at about the same time. Nearly every cell has an endothelial covering by day 12. The reticulum found between luteal cells is produced by the theca interna according to Solomons and Gatenby (126), but Corner (32, 33) stated that it is probably laid down by endothelial cells. Corner (35) investigated the distribution of the theca interna cells in porcine corpora lutea and found these cells scattered among the granulosa cells at day 18 of gestation. It was difficult, however, to differentiate theca interna cells after this time.

In the sow, Corner (31, 32) observed three principal types of luteal cells in the corpora lutea of pregnancy: (1) true lutein cells originating from the granulosa; (2) cells with smaller round or oval and more chromatic nuclei which appear on the periphery of the gland and along the connective tissue septa and (3) cells with a spindle shape and a cytoplasm which stained dark brown or purple with Mallory's stain. It was also noted that there were transitional stages among the three types.

In evaluating the physiologic aspects of the formation and persistence of the corpus luteum, it is desirable to consider briefly the morphologic development and retrogression of this gland. In the ewe, according to Warbritton (128), the corpus luteum develops from both the granulosa and theca interna, but the luteal cells of the mature gland appear to originate entirely from the former. Three types of cells (embryonic, normal and regressing) were noted and these represented three phases in the life cycle of a single luteal cell derived from the granulosa. The ovine corpus luteum reaches its maximum size at about the middle of the cycle (Casida and McKenzie, 28). The color of the gland changes from blood red in an early corpus luteum through translucent pink, opaque pink, cream and finally yellow.

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Corner (34) noted in the sow that, during the week following ovulation, corpora lutea attain a diameter of 8 to 10 mm. If the animal is pregnant, there is further growth until an average diameter of 10 to 11 mm. is reached. Histologically it has not been possible to distinguish between glands of the cycle and those of early pregnancy. At approximately day 16 of the cycle, a change occurs in the appearance of the corpus luteum in non-pregnant animals. By day 18 the diameter decreases to 6 mm., and the color changes from pink of active capillary circulation to whitish of scar tissue, indicating retrogressive changes in the nature of fibrous involution. Eventually all that remains of the site of an ovarian follicle, and subsequently a corpus luteum (either of a cycle or pregnancy), is a small mass of scar tissue, a corpus albicans.

McNutt (73, 74) studied the cyclic bovine corpus luteum as well as the corpus luteum of pregnancy and concluded that the luteal cells arise from both the granulosa and theca interna, but he added that many luteal cells exhibited intermediate characteristics and that the origin of these cells could not be stated with certainty. The newly formed corpus luteum may be identified on the fifth day when it protrudes above the level of the ovary. The young corpus luteum measures about 6 to 8 mm. in diameter. By 8 days it has increased to 18 to 20 mm., and when it is mature it measures 20 to 25 mm. The cyclic corpus luteum begins to regress about day 16 following estrus. There is, however, no marked reduction in size until the organ is 18 to 20 days old.

Melampy and Gay (83) made a study of the weight of both the ovary and its corpus luteum of pregnancy in the cow. The estimated age of the corpus luteum was based on the crown-rump length of the fetus. In the 298 cows examined, 90 percent of the ovaries, including the corpus luteum of pregnancy, weighed between 6 and 13 gm. Luteal weights ranged from 3.0 to 6.5 gm. and were approximately one-half of the total ovarian weight. No relationship was observed between the weight of the ovary or the corpus luteum and the stage of pregnancy in the cow. The mean luteal weights in grams were as follows: Angus 4.8, Hereford 4.7, Shorthorn 5.2 and Holstein 5.4. The mean weights for each breed were not significantly different.

According to Asdell (16) the corpus luteum becomes slightly larger during pregnancy than it is in the cycle, and the greatest size is attained at about 4 months, after which time the size and weight remain about constant. Retrogressive changes begin a little before parturition. According to Boyd (21) the time of its disappearance is from 30 to 90 days after calving, but occasionally it disappears earlier than 30 days.

Results of histological and histochemical investigations of the bovine corpus luteum have

have been reported by Weeth and Herman (129) and Foley and Reece (48). The latter investigated the gross and microscopic anatomy of the bovine corpus luteum between 25 and 45 days of gestation and stressed the variation in size, shape and staining qualities of the individual luteal cells. It was demonstrated that the luteal tissue was more compact and that the cells were larger and more rounding in shape, with the cytoplasm being more lightly stained between days 25 and 30. Moss et al. (95, 96) have reported studies dealing with the histochemistry of the bovine reproductive tract, including the corpus luteum. These investigators noted that the cyclic corpus luteum contained large amounts of alkaline phosphatase until about the thirteenth day of the cycle. This enzyme was very low or, except for capillary endothelium, absent in later stages of the cycle. Both theca and granulosa luteal cells contain phosphatase activity up to mid-cycle; it is first lost from the granulosa cells and later from the theca cells. The corpus luteum of cycling cows differs markedly from the corpus luteum of pregnancy with regard to the presence of phosphatase. The presence of phosphatase in the former and not in the latter would suggest that phosphatase is not concerned in the secretory activity of the corpus luteum but, rather, may be concerned in the initial stages of growth and development of this organ.

The luteal cells of bovine corpora lutea between 16 and 33 days of gestation have been classified into five types on the basis of their cytological characteristics by Foley and Greenstein (47). Type I cells represent "immature" luteal cells and Type II are mature cells which have reached their maximum size and development. Type III cells are believed to be in the initial stage of regression which continues through Type IV and terminates with Type V cells. Between 16 and 33 days of gestation, there is an increase in the number and the size of the Type II cells with a corresponding reduction in the Type I. These investigators concluded that the cytological changes in the bovine corpus luteum during early pregnancy coincide with advancing gestation and are related to the reproductive performance of the individual animal.

#### Physiologic Aspects

Stimulation of ovulable follicles in rats with luteinizing hormone (LH) causes the formation of corpora lutea, and the maintenance of these structures in a functional capacity is thought to be due to pituitary luteotropin, which is apparently identical with prolactin (Astwood, 18; Evans et al., 44, 45). Evidence for a pituitary luteotropin in the rat is particularly well demonstrated by maintenance of corpora lutea, but not follicles, for several months

following autotransplantation of the pituitary to the kidney (Everett, 46). Intact rats with a pituitary homotransplanted beneath the kidney capsule show a pseudopregnancy-like prolongation of the diestrus in progress at the time of transplantation, with a tendency for subsequent cycles to be prolonged (Quilligan and Rothchild, 104). The stimulus of mating is necessary for pseudopregnancy in the spontaneously ovulating rat and mouse. Pseudopregnancy follows ovulation with or without mating in induced ovulators, such as the rabbit and ferret. Corpora lutea capable of secreting progesterone form during non-fertile cycles in spontaneously ovulating domestic animals, such as the cow, sow, and ewe. Prolactin alone is unable to provide luteotropic effects in the rabbit (Hilliard *et al.*, 61; Kilpatrick *et al.*, 68, 69; Rennie *et al.*, 107); guinea pig (Aldred *et al.*, 1; Rowlands, 115); sow (Duncan *et al.*, 43; Sammelwitz and Nalbandov, 117); ewe (Denamur and Mauléon, 40; Moore and Nalbandov, 94); cow (Smith *et al.*, 125) or woman (Bradbury *et al.*, 22; Holmstrom and Jones, 63).

Rothchild (110) reported that lactation is maintained in oxytocin-treated hypophysectomized rats bearing pituitary autotransplants; thus, luteotropin (LTH) secretion does not depend on stimulation from the central nervous system (CNS). It was proposed that a CNS influence inhibits LTH secretion and that another CNS influence stimulates FSH and LH secretion; therefore, progesterone could maintain LTH secretion through its ability to suppress the CNS inhibition over LTH. A decrease in progesterone secretion allows the CNS inhibitor to increase its activity, thereby resulting in decreased LTH secretion. As a result, progesterone secretion is reduced to a lower level leading to complete cessation of both LTH and progesterone secretion and consequently to the regression of the corpus luteum. Progesterone injected into rats throughout the entire pregnancy or pseudopregnancy does not alter luteal function (Sammelwitz *et al.*, 116). The same lack of effect of treatment with progesterone on the size of the corpora lutea was observed in hypophysectomized rats with autotransplanted pituitaries. These findings demonstrate that progesterone does not inhibit the secretion of pituitary luteotropin in the rat (Rothchild, 111). Increased levels of progesterone may prolong the life of corpora lutea in the rat by maintaining secretion of a pituitary luteotropin (prolactin, LTH) (de Jongh and Wolthuis, 66; Rothchild, 112). Furthermore, the effect of hysterectomy in this species may be due to a deficiency or diminished secretion of LH, thus decreasing the luteolytic effectiveness of the pituitary gland. Estrogen treatment alone or combined with progesterone, depressed LH secretion in the rat, but progesterone treatment alone did not depress secretion of LH (Rothchild, 113). When

pituitary transplantation was combined with progesterone treatment, luteolysis occurred, but when pituitary transplantation was combined with estrogen treatment luteolysis usually did not result. Maintenance of prolactin secretion in the rat may depend upon progesterone and the failure of prolactin secretion may result from the depressive effect of LH upon progesterone secretion (Rothchild, 113). Thus, prolactin secretion and absence of LH appear necessary for persistence of the rat corpus luteum, and this will occur for prolonged periods when the pituitary is free of inhibitory affects of the CNS on prolactin secretion.

In 1961, Nalbandov proposed that the discharge of a pituitary luteotropin (defined as an unidentified substance or possibly LH) over a relatively short time (no longer than 2 to 3 days in guinea pigs and pigs) is sufficient to maintain corpora lutea for their normal life span during the estrous cycle. Furthermore, no further release of pituitary luteotropin occurs unless the female becomes pregnant, and, in this case, intrauterine events of implantation cause a secondary release of the pituitary luteotropin which may then be continuous throughout the gestation. These hypotheses were based on the assumption that the luteolytic effect of exogenous progesterone is not due to a direct action on progesterone of the formed corpora lutea and that sufficient levels of exogenous progesterone block secretion of a pituitary luteotropic substance. Sammelwitz *et al.* (116) demonstrated that high doses of progesterone injected into pregnant pigs from the time of ovulation until days 10 to 13 of gestation did not prevent formation of corpora lutea, whereas progesterone injections begun on days 12 to 16 of pregnancy resulted in complete and rapid destruction of the formed corpora lutea. Recently, Brinkley *et al.* (25) reported that exogenous progesterone beginning 1 or 2 days before ovulation, the day of ovulation, or 1 day after ovulation could not prevent the formation and maintenance of corpora lutea during the normal duration of the luteal phase of the cycle. Corpora lutea in these progesterone-treated gilts were normal as indicated by chemical determination of progesterone content of the tissue at slaughter. From these observations in the pig (Brinkley *et al.*, 25), it was concluded that the pituitary luteotropin needed for corpus luteum maintenance is released either before or simultaneously with the release of LH and that this hormone is not required beyond the initial "impetus" for formation of functional corpora lutea. Du Mesnil du Buisson and Léglise (88) found that corpora lutea formed in pigs hypophysectomized only a few hours after the first signs of estrus. Also, corpora lutea were morphologically normal, contained normal concentrations of progesterone, but were generally smaller at days 13 and 14

of the cycle when hypophysectomies were performed during early luteal phases of the cycle. These results tend to support the contention that a pituitary luteotropic secreted during the initial phases of the estrous cycle may be sufficient for the formation and maintenance of the corpora lutea of that cycle. In progestin-treated nonpregnant gilts with follicular growth induced by pregnant mare serum (PMS) treatment, a single injection of an ovulatory-dose of human chorionic gonadotropin (HCG) was sufficient to cause ovulation and formation of normal corpora lutea, as indicated by progesterone content (Brinkley *et al.*, 24). However, daily injections of HCG in progestin-blocked pregnant pigs will support morphologically normal corpora lutea for as long as 16 days, but the luteal tissue is not physiologically normal as shown by reduced progesterone concentrations. Thus, HCG apparently is without luteotropic action in the pregnant animal. It was concluded that corpora lutea of pregnancy, unlike those corpora lutea of the estrous cycle, are supported by a continuous or sustained release of a luteotropic substance.

Using prepubertal lambs, Denamur and Mauléon (40) found both that 1 to 3 ovulations could be induced with injections of PMS and chorionic gonadotropin and that corpora lutea formed were morphologically and histologically normal. These corpora lutea remained functional until 12 days post-ovulation; the onset of luteal regression occurred between the 12th and the 16th days, and regression was complete by the 20th day. Similar development, maintenance and regression of corpora lutea occurred in treated lambs hypophysectomized on the day of induced ovulation.

Hypophysectomy or section of the pituitary stalk does not terminate pregnancy in ewes when these operations are performed at various stages from the 42nd to 90th days of gestation (Cowie *et al.*, 36; Denamur and Martinet, 38). Gestation also continues when ovariectomy precedes hypophysectomy at mid-gestation (Denamur and Martinet, 38). In goats, however, hypophysectomy or pituitary stalk section is followed by abortion within a few days (Cowie *et al.*, 36). Luteal regression also occurs following hypophysectomy in pseudopregnant ferrets, but stalk section of the pituitary is compatible with full development of corpora lutea at least during the first month of pseudopregnancy (Donovan, 41). The isolated pituitary in this species may store and secrete some luteotropin; however, the corpora lutea eventually regress. It was further suggested that estrogen as well as a pituitary luteotropin may be required for luteal maintenance in the ferret.

Results of investigations have shown that exogenous estrogen influences the luteal function in various species (Amoroso and Finn, 2). Kidder *et al.* (67) injected gilts with 3 mg. diethylstilbestrol on either the 6th, 11th or

16th day of the cycle and observed cycle lengths of 19, 78, 25, 60 and 18 days respectively. Corpora lutea were maintained until slaughter at 34 days post-estrus in 19 of 20 gilts injected daily with 7.5 or 15 mg. of estrone or estradiol-17 $\beta$  per day beginning on day 11 of the cycle (Gardner *et al.*, 49). Bowerman *et al.* (20) have investigated the quantities of urinary estrogen metabolites from gilts during the estrous cycle and pregnancy and examined the possibility of a uterine influence on the metabolism of estrogen by comparing urinary metabolites from intact and hysterectomized and from ovariectomized and ovariectomized-hysterectomized gilts following administration of exogenous hormones. Quantities of estrone were low in urine at several stages from hysterectomized animals in comparison to cycling and pregnant animals. Rombauts and du Mesnil du Buisson (109) recently reported that urinary excretion of estrone remained low in sows following hysterectomy on day 70 of gestation. Results from experiments with ovariectomized and ovariectomized-hysterectomized animals did not show any marked influence of the uterus or progesterone-stimulated uterus on the manner in which injected estradiol benzoate was eliminated in the urine (Bowerman *et al.*, 20). The total amount of injected estradiol benzoate recovered in the urine of these animals as estrone ranged from 39 to 60 percent during a 4-day period. The estimates for estradiol were consistently low and without marked variation in any of the urine samples studied. Estriol was not detected. These results suggest that the uterus does not influence the quantity or kind of estrogen metabolites of gilt urine.

Exogenous estrogen maintains corpora lutea in the hypophysectomized rabbit (108), intact lamb (39) and sow (49,86) and has an apparent luteolytic action in the cow (51, 53, 72, 132). In the hypophysectomized rat, exogenous estrogen causes an increase in the number of ovarian follicles and the amount of granulosa (101, 102, 130). Corpora lutea form in these rats following injections of PMS or HCG. According to Denamur and Mauléon (39), estradiol given from the day of induced ovulation in lambs maintained morphologically and histologically normal corpora lutea for about 50 days. Estrogen treatment did not maintain corpora lutea in lambs hypophysectomized on the day of induced ovulation; luteal regression was complete within 20 days. Similar results have been obtained in the gilt by du Mesnil du Buisson (86). Estradiol benzoate, at doses sufficient to maintain corpora lutea for prolonged periods in the intact gilt, failed to maintain corpora lutea following hypophysectomy. Daily injections of the estrogen were initiated either 2 days before or 6 days after hypophysectomy in the early luteal phase of the cycle (days 6 or 8) and total luteal regression occurred within 22 days after the

previous estrus. Absence of luteal maintenance by estrogen in hypophysectomized lambs and gilts may indicate an indirect action of this hormone on the life span of the corpus luteum.

Results of recent experiments on the effect of injecting various pituitary hormones on luteal function generally have been negative in sheep and swine. Homogenates of fresh, whole pituitary glands from gilts at different stages of the estrous cycle and gestation did not alter the life span of corpora lutea *in vivo* or affect progesterone synthesis by swine luteal tissue *in vitro* (Anderson *et al.*, 9; Duncan *et al.*, 43). Short *et al.* (122) found that progesterone secretion of the corpus luteum was unaffected on the 9th and 15th day of the estrous cycle by injections of ovine prolactin, ovine LH, or chorionic gonadotropin. Furthermore, ovine FSH, growth hormone (GH), ACTH, thyrotropic hormone (TSH), PMS, fresh and acetone-dried ovine pituitaries or endometrial extracts failed to alter the secretory activity of the ovine corpus luteum, over a short period of time at the 9th day of the estrous cycle (Short, 121; Short *et al.*, 122). Denamur and Mauléon (39) reported that bovine prolactin injected daily from the day of induced ovulation for 20 days did not maintain corpora lutea in intact lambs (up to 2,400 I.U. prolactin per day) or in lambs hypophysectomized on the day of ovulation (1,200 I.U. prolactin per day). In hypophysectomized rabbits (Kilpatrick *et al.*, 68, 69; Rennie *et al.*, 107) and in guinea pigs (Rowlands, 115) ovine prolactin has failed to maintain corpora lutea. However, ovine LH was luteotropic in hypophysectomized rabbits (Kilpatrick *et al.*, 68, 69).

PMS, HCG or LH in the incubation medium stimulates *in vitro* synthesis of progesterone of corpora lutea from the ewe (Legault-Démare *et al.*, 70); cow (Mason *et al.*, 81; Savard and Casey, 119; Armstrong *et al.*, 12; Armstrong, 11; Marsh and Savard, 76, 77); rat (Armstrong *et al.*, 13), but little stimulating effect on progesterone synthesis from swine luteal tissue (Duncan *et al.*, 43; Neill *et al.*, 100). Increase in synthesis of progesterone by bovine luteal slices was effected by TPN and glucose-6-phosphate; DPN and DPNH did not alter this process. LH increased the incorporation of  $C^{14}$  acetate into progesterone 3 to 5 times, whereas addition of NADP and glucose-6-phosphate caused an 8-to 15-fold increase in progesterone production with no increase in the incorporation of  $C^{14}$  into the steroid (Marsh *et al.*, 75; Mason *et al.*, 81; Savard and Casey, 118). The minimum effective concentration of LH required for increased synthesis of progesterone *in vitro* was 0.01 - 0.02 mcg./gm. of bovine luteal tissue (Mason and Savard, 80). Prolactin did not produce a stimulatory effect on *in vitro* progesterone synthesis (Mason *et al.*, 81) and the stimulating effect of FSH was attributed to small amounts of LH in the preparation (Mason and Savard, 81).

Microgram amounts of ovine LH in the incubation medium increased *in vitro* phosphorylase activity of luteal slices from pregnant cows (Marsh and Savard, 76). Luteinizing hormone not only maintained the high initial level of phosphorylase activity but was capable of increasing this activity after it had reached relatively low levels. Prolactin, ACTH, peroxide-in-activated LH and adenosine 3', 5' -monophosphate (3', 5' -AMP) were ineffective in stimulating phosphorylase activity, whereas ovine FSH and ovine GH were stimulatory. The stimulating effects of the latter hormones were explained as due to LH contamination. A corresponding increase in *in vitro* progesterone synthesis and phosphorylase activity occurred in bovine luteal slices when measured in the same luteal tissue. Marsh and Savard (77) reported that the addition of 3', 5' -AMP to incubating slices of bovine corpus luteum increased the rate of progesterone synthesis without increasing the phosphorylase activity of the tissue. The 2- to 3-fold stimulation by 3', 5' -AMP of the amount (mcg.) of progesterone synthesized was accompanied by a similar increase in the incorporation of acetate- $C^{14}$  into the steroid. Results of incubating active and involuting bovine corpora lutea surgically removed at different stages of the estrous cycle were reported by Armstrong *et al.* (12). Maximal progesterone synthesis occurred from cows 4 to 13 days post estrus, declined gradually until day 18 and decreased to undetectable levels at day 19. Addition of LH to the incubation medium increased progesterone synthesis through day 18, but was ineffective on corpora lutea obtained from day 19 or later. Progesterone synthesis in corpora lutea obtained from day 19 or later was partially restored by addition of pregnenolone or of TPN plus glucose-6-phosphate to the incubation medium. TPN plus glucose-6-phosphate were only minimally effective in stimulating progesterone synthesis in corpora lutea from early stages of the estrous cycle (Armstrong, 11). It is suggested that possibly TPNH is not rate limiting in fresh luteal tissue but is rate limiting if tissue is deprived of oxygen or nutrient supply. Inactive corpora lutea were not deficient in stores of cholesterol but may be deficient in the enzyme system necessary for conversion of this probable precursor in progesterone synthesis. Simmons and Hansel (124) investigated luteal progesterone from heifers given different hormone treatments and suggested the occurrence of a specific bovine luteotropin hormone which is not bovine growth hormone, equine LH or ovine prolactin.

Armstrong and Greep (14) observed a stimulatory effect of LH upon the uptake of glucose by slices of luteinized rat ovaries and two-thirds of the utilized glucose was converted to lactic acid (Armstrong, 10). Lactic acid formation was stimulated by *in vivo* LH and in

proportion to its stimulation of glucose uptake. In these experiments FSH and prolactin did not stimulate glucose uptake except at levels which could be caused by LH contamination. When the LH was given intravenously to rats 4 hr. prior to autopsy, there was a significant increase in the conversion of glucose to CO<sub>2</sub> and lipid, as well as an overall increase in the uptake of glucose by the luteal slices. However, when LH was added directly to the incubation medium there resulted an increased progesterone synthesis without affecting the rate of glucose metabolism (Armstrong et al., 13). Increased glycolysis appeared to be an effect rather than a cause for the increased synthesis of luteal progesterone. Armstrong (11) found that stimulation of glycolysis following LH was involved in the replenishment of stores of lipid precursors which have been depleted as a result of the stimulatory action of LH upon progesterone synthesis. It was proposed that LH possibly mobilizes lipid stores for progesterone synthesis by the corpora lutea and these lipid stores are replenished both from cholesterol and long chain free fatty acids brought to the tissue by the plasma.

In the ewe, corpora lutea, induced by ovine pituitary extract at different luteal phases of the estrous cycle, regress at the same time as the natural corpora lutea, even after the natural corpora lutea have been removed (Inskeep et al., 65). It was concluded that the life span of corpora lutea in this species is determined by a factor extrinsic to the gland itself. However, in the gilt, induced and natural corpora lutea of different ages on the same ovary retain their luteal life spans of approximately one estrous cycle (Neill and Day, 99). Thus, an intrinsic mechanism determining the life of the corpus luteum possibly at the time of luteal formation is likely in this species. Both natural and induced corpora lutea persist in hysterectomized gilts.

There appear to be species differences in the relationship between the level of ovarian and subsequent luteal function and the degree of pituitary activity (Nalbandov, 97). For example, the events of ovulation, whether induced or spontaneous, are sufficient to cause the formation and maintenance of corpora lutea in the pig for a period of time characteristic of this species. In the ewe, however, the physiologic events leading to the development of these glands do not appear adequate for their maintenance without supplemental pituitary stimulation. It is possible, in species producing functional corpora lutea, that luteolysis during the estrous cycle is initiated as a result of an inhibitory humoral or neurohumoral stimulus of uterine origin acting on the anterior pituitary by way of the CNS. This action could lead either to inhibition of hypophysial luteotropin or alteration in gonadotropic complex activity and would thereby

induce luteal regression. During pregnancy and following hysterectomy, this uterine inhibition is absent in some species and as a result functional corpora lutea persist (Nalbandov, personal communication).

Increasing attention has been given to the role of the uterus in alteration of pituitary and gonad function. Maintenance of the functional corpus luteum during at least the initial phases of gestation is well recognized in several species (Amoroso and Finn, 2). Hysterectomy alters ovarian function which results in persistence of the corpus luteum in the guinea pig (Butcher et al., 27; Loeb, 71; Rowlands, 114); ewe (Denamur and Mauléon, 39; Moor and Rowson, 91; Wiltbank and Casida, 131); sow (Anderson et al., 6; Anderson et al., 7; du Mesnil du Buisson and Dauzier, 87; Neill and Day, 99; Spies et al., 127) and cow (Anderson and Bowerman, 4; Anderson et al., 3; Armstrong and Hansel, 15; Wiltbank and Casida, 131; Wiltbank et al., 133). The corpora lutea following hysterectomy are maintained for a period approaching or exceeding the length of gestation in these species. However, that same operation has no apparent effect on ovarian function in the ferret, opossum, monkey, woman or unmated rat, mouse and rabbit (Amoroso and Finn, 2; Anderson et al., 5). Hysterectomy performed at different phases of the estrous cycle has been reported recently in the gilt (Anderson et al., 7); guinea pig (Rowlands, 114); ewe (Moor and Rowson, 91) and at different stages of pseudopregnancy in the rat (Melampy et al., 82). Silbiger and Rothchild (123) suggest that hysterectomy in the rat results in decreased secretion of both FSH and LH and that a decrease in the luteolytic effectiveness of the pituitary is associated with the diminished secretion of LH.

In the gilt, removal of the uterus at estrus or days 5, 10, 14 and in a majority at day 16, resulted in formation and maintenance of corpora lutea. Estrus and ovulation occurred within a few days when the uterus was removed at day 18. Although morphologic changes associated with luteal regression occurred in hysterectomized gilts during the interval between days 16 and 18, the presence of a luteolytic or absence of luteotropic action may be initiated at an earlier stage of the cycle. Hysterectomy as late as day 15 of the cycle prevented impending estrus and ovulation in guinea pigs (Rowlands, 114) and, in ewes (Moor and Rowson, 91), arrested the involutionary changes in luteal cells, provided the corpus luteum was still functional at the time of the operation. In rats, hysterectomy on days 5, 9 and 11 of pseudopregnancy resulted in prolongation of the life span of corpora lutea to approximately that of normal gestation, whereas luteal regression was initiated somewhat earlier when the uterus was removed at day 13 (Melampy et al., 82). Enucleation of the persisting corpora lutea



in hysterectomized gilts (Anderson et al., 9) and heifers (Anderson and Bowerman, 4) is followed within a few days by estrus, ovulation and maintenance of the newly formed corpora lutea.

Secretion of a hypophysial luteotropin for maintenance of corpora lutea for prolonged periods in the hysterectomized ewe and gilt is evident by luteal regression following hypophysectomy in these animals. Denamur and Mauléon (39) found that corpora lutea were in the process of regression or completely regressed 20 days after hysterectomizing and hypophysectomizing ewes on the day of ovulation. Furthermore, luteal regression was complete within 20 days in ewes hypophysectomized 20 days after hysterectomy. Du Mesnil du Buisson and Léglise (88) reported that luteal regression began within 5 days and was complete by 10 to 11 days in gilts previously hysterectomized during the early luteal phase (days 4 to 8) and hypophysectomized 22 days after the beginning of estrus. Similar results were obtained when gilts were hypophysectomized 29, 46, 97 and 99 days after hysterectomy (du Mesnil du Buisson, 86). Complete luteal regression also occurred within 20 days when hypophysectomies were performed at estrus and followed by hysterectomies in the early luteal phase of the cycle (du Mesnil du Buisson, 86). Maintenance of corpora lutea in the hysterectomized ewe and gilt is not possible in the absence of the pituitary. Persistence of corpora lutea following hypophysectomy in previously hysterectomized guinea pigs indicates that removal of the uterus does not affect luteal function by secretion of a pituitary luteotropin in this species (Rowlands, 115). In experiments of Deanesly and Perry (37), both progesterone and reserpine caused regression of corpora lutea in hysterectomized guinea pigs. They concluded that in the guinea pig the corpora lutea of hysterectomy do not function independently of the pituitary.

Short (121) has proposed a system of dual control of the life span of the corpus luteum for the ewe by a pituitary luteotropin and a uterine luteolysin. In this scheme, a pituitary "on" mechanism would stimulate and maintain the corpus luteum life span but perhaps not its secretory activity by a single release of a pituitary luteotropin at the time of ovulation. However, the luteotropin may be released into the circulation continuously. A uterine "off" mechanism would determine the length of the estrous cycle by providing a luteolysin. Of the two mechanisms, the uterine luteolysin would have the overriding effect.

Subtotal hysterectomy in the guinea pig (Butcher et al., 27); gilt (Anderson et al., 6); heifer (Anderson et al., 8) and ewe (Moor and Rowson, 91) results in luteal regression and continuation of estrous cycles. However, the duration of the estrous cycle in these species is affected by the proportion of uterus

removed. Recent investigations in the ewe by Moor and Rowson (91) showed that one-half of the cycles were extended beyond 20 days when one uterine horn was removed, whereas one-fourth of the cycles were extended when only the distal half of one horn was removed. Uterine and endometrial autotransplants in the guinea pig (Butcher et al., 26) and uterine autotransplants in the pig (Anderson et al., 7; du Mesnil du Buisson and Rombauts, 89) results in continuation of estrous cycles and, in rats, (Melampy et al., 82) reduces the duration of pseudopregnancy. A functional endometrium, as evaluated histologically, appears to be necessary for luteal regression in these species.

Unilateral regression of corpora lutea has been observed on the side of the uterine fragment in partially hysterectomized gilts (du Mesnil du Buisson, 85). In gilts mated after one uterine horn was severed from the uterine body, early failure of pregnancy occurred in the intact horn (du Mesnil du Buisson, 84). Gestation continued in these animals if the non-gravid horn was removed by day 14, but pregnancy was terminated when unilateral hysterectomy was postponed until after day 16 (du Mesnil du Buisson, 84). Unilateral luteal regression occurred on the side of the non-gravid horn in gilts that became pregnant with either a whole or anterior half or quarter of a sterile horn present (Rathmacher and Anderson, 106). Normal pregnancy and maintenance of corpora lutea on both ovaries occurred in unilaterally hysterectomized animals. It is apparent that the non-gravid horn is responsible for the termination of pregnancy through a luteolytic action which it initiates. The physiologic basis of this action is unknown, but it is possible that ovarian-uterine vascular relationships may be involved in the initiation of this luteolysis.

The duration of anestrus was prolonged more than 100 days in 6 of 8 intact gilts injected with an optimum total of 35 mg. of estradiol benzoate over a 7-day period beginning on days 7, 9 or 12 of the cycle (du Mesnil du Buisson, 86). Estrogen treatment beginning at day 14 had no effect on the length of the estrous cycle. Corpora lutea were maintained in both ovaries in estrogen-treated unilaterally pregnant gilts with one empty uterine horn at 30, 55 or 90 to 103 days of gestation. Therefore, estradiol benzoate suppresses luteolytic action, not only during the estrous cycle, but also in unilaterally pregnant gilts in which the non-gravid uterine horn would otherwise effect a unilateral regression of corpora lutea on the side of the non-gravid horn. Du Mesnil du Buisson and Rombauts (90) found that gestation continued in a majority of gilts in which all of the uterus was removed except one embryo and its corresponding portion of uterine horn on the 12th day of pregnancy. When a certain number of



embryos were removed with or without the corresponding portion of the uterine horns around the 40th or 80th day of gestation, pregnancy continued in most animals in which some embryos with corresponding uterine horns were removed, whereas very few gilts remained pregnant when only some embryos were removed. The portion of empty uterine horn apparently had a negative influence on maintenance of pregnancy after the first 40 days, but uterine luteolytic activity of the empty horn was not evident on the corresponding ovary at this time.

Surgical removal of embryos during the first 12 days in the ewe resulted in subsequent normal estrous behavior, whereas removal of embryos on the 13th and 14th days after estrus resulted in a marked extension of the luteal life span (Moor and Rowson, 91). Furthermore, transfer of 12 or 13 day embryos to the uterus of non-pregnant recipient ewes on the 12th day of their cycle resulted in normal pregnancies. Embryonic loss frequently occurred when 13 day embryos were transferred to day 13 recipient ewes. It was suggested that the life span of the corpus luteum in this species was not irrevocably determined until after the 12th day of the estrous cycle.

Estrous cycles are altered by uterine distention in the rat (Selye, 120); guinea pig (Donovan and Traczyk, 42; Moore, 92); cow (Armstrong and Hansel, 15; Chatterjee and Luktuke, 29; Hansel, 54; Hansel and Wagner, 55; Yamauchi and Nakahara, 134) and ewe (Inskeep et al., 64; Moore and Nalbandov, 93; Nalbandov et al., 98) but not in the pig (Anderson, 3). Uterine innervation in these species can play a role in changing ovarian function, possibly by affecting central nervous system activity and thereby pituitary hormone secretion or possibly by a more direct action on the ovary. However, mechanisms by which uterine distention modifies the cycle may be unrelated to those mechanisms affecting the physiological processes in the formation, maintenance and regression of the corpus luteum during the normal estrous cycle or during pregnancy.

#### Summary

Follicular growth and maturation are dependent upon pituitary gonadotropins; ovulation is followed by further proliferation of granulosa and theca cells which form the corpus luteum. In the ewe and sow the ovary is capable of ovulation when the pituitary is removed at or just prior to ovulation, the corpus luteum which develops subsequently is maintained for the approximate duration of the estrous cycle. It has been proposed that perhaps a pituitary luteotropin, if required, is secreted for a brief period at the time of ovulation and is sufficient for the development

of the corpus luteum of that cycle. Luteinizing hormone is required for the processes of follicular maturation and ovulation as indicated by experimental induction of ovulation and by depletion of pituitary gonadotropin content prior to ovulation. The necessity for a luteotropin, whether this is luteinizing hormone or an unidentified pituitary luteotropin, is not clearly established for the initial development of the corpus luteum during the estrous cycle. Maintenance of the corpus luteum in the pregnant or hysterectomized animal is dependent upon an apparent continuous requirement of pituitary gonadotropin with luteotropic action.

The role of the uterus in altering the life of the corpus luteum in the cow, sow and ewe is evident by extension of the luteal life span during pregnancy and following hysterectomy, and, in the case of the sow, luteolytic action of a non-gravid portion of the uterus in partially hysterectomized or unilaterally pregnant animals. The physiologic basis of unilateral regression of corpora lutea is unknown. It is possible that ovarian-uterine vascular relationships may be involved in the initiation of this luteolysis. In subtotally hysterectomized animals, estrous cycles occur, however, the duration of the cycle is altered by the proportion of uterus removed. Estrous cycles occur following autotransplantation of the uterus in the guinea pig and sow and in rats the duration of pseudopregnancy is reduced. A functional endometrium appears necessary for luteal regression in these species. It may be that in the cycling female the uterus maintains a positive inhibition of pituitary luteotropin secretion and during pregnancy or following hysterectomy, this inhibition is lacking; hence, the persistence of corpora lutea.

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