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Minireview

Selection of the Dominant Follicle in Cattle[1]

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INTRODUCTION

On the basis of gross and histologic study of ovaries, it was proposed in 1960 that two waves of follicular activity occurred during bovine estrous cycles [1]. The two-wave hypothesis was not tested and languished for more than 20 years. Results of a histologic study in 1981 [2] were consistent with the two-wave hypothesis. However, results of a 1983 study [3], involving measurement of follicles and steroid assays of blood and follicular fluid, led to the conclusion that there were three follicular waves, and each resulted in a dominant follicle. A review of follicle turnover in cattle in 1986 [4] concluded that, rather than two or three waves, progressively larger follicles developed with rapid atresia of each until an ovulatory-sized follicle appeared. The slow progress and divergent conclusions attest to the challenge inherent in studying follicle development.

A technologic breakthrough was reported in 1984 [5] and has led to clarification of the nature of bovine folliculogenesis for follicles with antral diameters of ≥ 3 mm. Transrectal ultrasonic imaging provided a means for repeated, direct, noninvasive monitoring and measuring of follicles regardless of their depth within the ovary. Profiles of mean numbers of follicles for various diameter groups were bimodal during the estrous cycle [6] and early pregnancy [7], supporting the two-wave hypothesis. The power of the technology was expanded in 1988 with reports from three laboratories [8–11] on tracking or monitoring daily diameter changes of individual follicles. One laboratory [12] found mostly (81%) two-wave estrous cycles, whereas the others [10, 11] found mostly (80%) three-wave cycles. Some of the factors found to affect the number of waves per estrous cycle include dietary intake [13], parity, and lactational status [14]. Furthermore, the diameter attained by the dominant follicle is affected by stage of the estrous cycle [12] and pregnancy [15]. Varied numbers of waves and diameters of the dominant follicle and their sensitivity to a wide array of factors are challenging aspects of this research area.

In addition to clarifying the number of waves per estrous cycle, the ultrasound tracking studies have characterized the composition of follicular waves [16]. The onset of the first wave of an estrous cycle is detected as a group of 4-mm follicles just before the day of ovulation. During the next few days, one of the follicles becomes dominant, and the others become subordinate. A second wave emerges at about 10 days postovulation and, for three-wave cycles, is followed by another wave at 16 days. The ovulatory follicle originates from the final wave. The wave phenomenon is under intensive investigation in many laboratories; reviews or original reports with large review sections are available [12, 14, 16–20]. The interest in this area is motivated by the desire to solve the long-time mystery involving the mechanisms underlying the selection of a specific follicle for ovulation in monovular species and the need for basic information for designing synchronization and superovulation protocols [21]. Even with ultrasound technology to track individual follicles, resolution of the selection phenomenon is proving to be as elusive as the earlier documentation and characterization of follicular waves.

This report presents a conceptual model of the current status of knowledge on the selection phenomenon in cattle. The model is limited to the period extending from the beginning of a follicular wave to the early growth phase of the selected dominant follicle and does not include the factors controlling the diameter achieved by the dominant follicle or its maintenance and regression. The model will serve as a guide for the discussion of systemic and cellular aspects of the selection phenomenon. This minireview is not exhaustive, but amalgamates the contributions of many laboratories. During development of the model, voids appeared because of the lack of the desired information in the literature. The missing information was obtained by reanalyses of data that had been used for previous publications from our laboratory. The previous reports did not present the data in a manner compatible with construction of the model. The reanalyzed data were from ultrasonic scanning of 28 follicular waves every 8 h [22], and scanning of follicles and assay of circulating FSH every 24 h [23].

EARLY DEVELOPMENT AND DEVIATION OF FOLLICLES

Time of emergence of a follicular wave is defined as the last day or examination (if more than one examination per day) the future dominant follicle was 4 mm and is designated by Day 0 or Examination 0 throughout this report. The follicles are depicted in the model (Fig. 1) by circles. The smallest circles represent 3-mm follicles. The depicted number and distribution of the cohort of growing 3-mm

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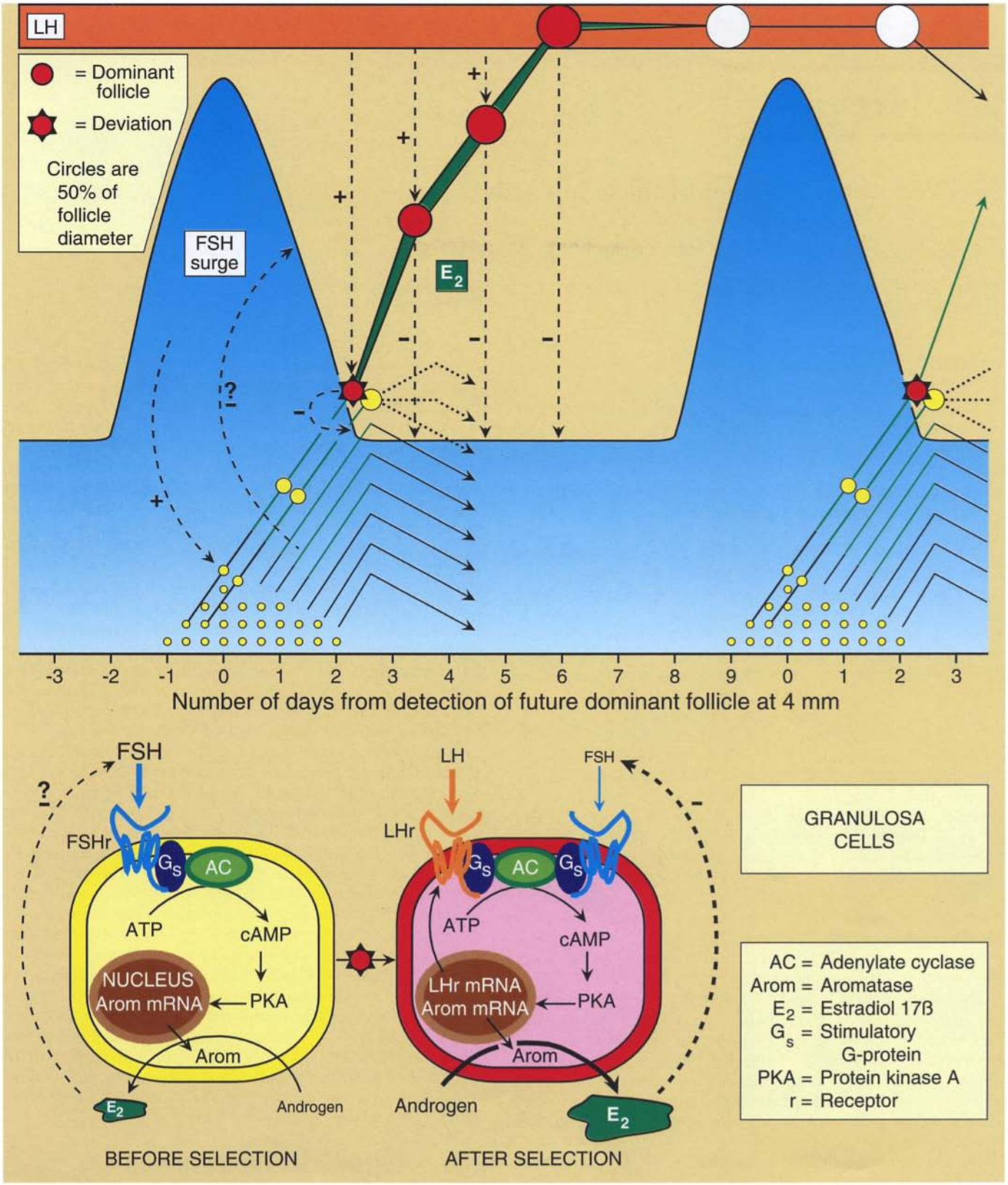

FIG. 1. Schematic model of the postulated nature of the follicle-deviation mechanism in cattle, depicting the systemic aspects (top) and cellular aspects (bottom). Reference to the model is made throughout the text.

follicles during the emergence of the wave are based on the reanalysis of data obtained every 8 h. The number of examinations at 8-h intervals that encompassed the emergence of all growing follicles at 3 mm was 10.0 ± 0.5 (mean ± SEM; equivalent to 3.3 days) and extended from Examination −3.1 ± 0.3 to Examination 6.0 ± 0.6. A mean of 24 (range, 8–41) growing 3-mm follicles was detected per wave, and their viability was established by their subsequent growth to ≥ 4 mm. The maximum diameters attained by the 24 follicles were 4 mm (11 follicles), 5 mm (6 follicles), and ≥ 6 mm (7 follicles).

Time of deviation is defined as the beginning of the greatest difference in growth rates (diameter changes between adjacent examinations) between the two largest follicles at or before the examination when the second-largest follicle reached its maximum diameter. The definition was developed to allow objective assignment of the time of deviation in individual waves. Either deviation of follicles is a major event in the selection process, or the terms deviation and selection are synonymous. In retrospect, the following two faulty assumptions have hampered progress in studies of follicle selection: 1) the follicles of the cohort are equivalent in diameter at the time of deviation, and 2) between Days 0 and 4 the dominant and largest subordinate follicles diverge gradually in diameter. In regard to the first assumption, the future dominant follicle appeared as a 3-mm follicle earlier (57%) than, at the same time (26%) as, and later (17%) than the largest subordinate follicle in the reanalysis of data obtained at 8-h intervals. On average, the future dominant follicle emerged at 3 mm at Examination −2.1 ± 0.2, which was 6 h earlier ($p < 0.03$) than for the future largest subordinate follicle (Examination −1.4 ± 0.3) and 10 h earlier ($p < 0.03$) than for the future second-largest subordinate follicle (Examination −0.8 ± 0.4). In the reanalysis of data obtained every 24 h from 33 follicular waves, the dominant follicle was larger (76% of waves) than, the same diameter (21%) as, or smaller (3%) than the largest subordinate follicle at the beginning of deviation of the two follicles. These findings indicate that the selected dominant follicle often has a size advantage, and therefore the model depicts the dominant follicle as the one that is first to develop to a decisive diameter or stage. Occasionally, however, a future subordinate follicle is larger initially than the future dominant follicle but grows at a slower rate so that it is not the first to reach the decisive stage (Fig. 2c). Presumably, the duration of the decisive stage is short so that the deviation mechanism is completed before the arrival of the next follicle to a similar stage. Hormonal events can occur rapidly, as indicated by the following examples: 1) the peak of an LH pulse was followed by the peak of an estradiol pulse within 15 min [24] and 2) lowering the systemic concentrations of progesterone increased the frequency of LH pulses and concentrations of estradiol within 6 h [25].

The faulty assumption that follicle divergence is a gradual process was a product primarily of our laboratory and resulted from misinterpretation of results [12, 16, 22]. When data were normalized so that the future dominant follicle of all waves emerged on a common day, mean diameters of the retrospectively identified dominant and largest subordinate follicles gradually diverged over the next 4 days. The interpretation was that biologic selection occurred on or before the day of emergence and was manifested by subsequent differences in growth rates of the two follicles. In the reanalysis of data obtained every 24 h, the result of normalizing the two largest follicles to the day of

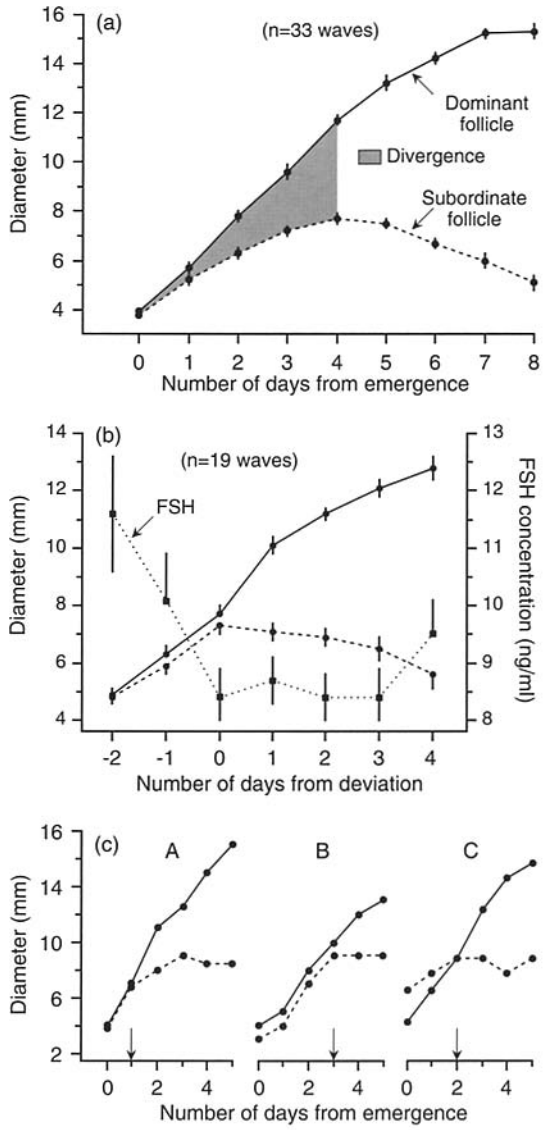

FIG. 2. **a**) Mean profiles for the dominant and largest subordinate follicles normalized to the day of emergence of the retrospectively identified dominant follicle at 4 mm. The average growth rates gradually diverge between the two follicles. **b**) Mean profiles for the dominant and largest subordinate follicles normalized to the day of deviation of the two largest follicles in individual waves and the associated FSH concentrations. The growth rates before deviation did not differ significantly between the future dominant and subordinate follicles. The FSH concentrations reached a nadir on the day of deviation. **c**) Examples of the follicle growth profiles for three individual waves. The arrows indicate the chosen days of deviation. From reanalyses of published data [22, 23].

emergence was compared to the result of assigning a day of deviation to each wave and then normalizing to the day of deviation (Fig. 2). When data were normalized to the day of emergence, there was a gradual divergence in mean growth rates of the two largest follicles for 4 days. When data were normalized to the day of deviation, there were no significant differences in growth rates between the two follicles until deviation began. Thus, the mean gradual divergence over the first 4 days after emergence was a reflection of deviation in growth rates between the dominant and largest subordinate follicles at varied times in individual waves. The mean day at the beginning of deviation in growth rates of the two largest follicles was Day 2.8, when the future dominant follicle was a mean of 8.5 mm and the

largest subordinate follicle was 7.2 mm. These means were used in constructing the model. Inspection of individual follicle profiles indicated that biologic variation is well represented by deviation. Occasionally one follicle appeared to become dominant, as indicated by the extent of deviation, but then lost its apparent propitious position and was replaced by a subordinate follicle. If this suspected vacillation occurs occasionally, it provides an added challenge to the researcher.

All growing or viable follicles are capable of becoming dominant, as indicated by the following: 1) initiation of an FSH treatment protocol early in the wave stimulates many follicles to attain the diameter of dominant follicles [26]; 2) a follicle randomly selected from a pool of 5-mm follicles at the beginning of a wave can be directed toward dominance by destroying all other 5-mm follicles [27]; and 3) even after deviation in growth rates between the two largest follicles, the subordinate follicle can remain viable for a day or two and can assume dominance, if the original dominant follicle is destroyed [28, 29].

Normalizing follicle data to the day of deviation between the retrospectively identified dominant and largest subordinate follicles suggested the presence of a transient growth spurt by the selected dominant follicle (Fig. 2). The growth spurt is depicted in the model, although it is not clear whether the spurt is a biologic event or an artifact inherent in choosing the time of deviation in individual waves. Deviation was characterized by the immediate cessation of growth of the largest subordinate follicle (30% of 33 waves) and by a slower rate of growth for 1–4 days before the subordinate follicle attained maximum diameter (70% of waves). The varied paths followed by the largest subordinate follicle after deviation are indicated by dotted lines in the model. Other subordinate follicles begin to regress at approximately the same time as the largest subordinate follicle. In the reanalyzed 8-h data, follicles that grew from 3 to 4 mm early in the wave usually grew to $\geq$ 6 mm, whereas follicles that attained only 4 or 5 mm usually emerged later in the wave ($p < 0.05$). These findings are reflected, in principle, by the bent arrows in the model.

FSH SURGES AND STIMULATION OF WAVES

Although FSH is, by definition, the follicle-stimulating hormone, a temporal association between a surge in circulating FSH concentrations and emergence of each follicular wave was not demonstrated until 1992 [23]. The documentation was aided by normalizing the waves and associated FSH values to the day of emergence of the future dominant follicle. The association between an FSH surge and emergence of a follicular wave has been confirmed independently for the estrous cycle [22, 30, 31] and has been shown in calves as young as 6–8 mo [32, 33] and during pregnancy and the postpartum period [15]. The peak of the FSH surge occurs at or near the time when the future dominant follicle of the resulting follicular wave has a mean diameter of only 4 mm [25]. Apparently, the first appearance of growing 3-mm follicles of a wave occurs during the incline in the FSH surge and continues until the FSH declines to basal concentrations, as shown in the model. In addition to the temporal association between FSH surges and the stimulation of follicular waves, the results of experimental manipulations are consistent with a cause-and-effect relationship, including the following: 1) in vitro FSH stimulation of granulosa cells [34] and preantral follicles [35, 36], 2) in vivo stimulation of follicles by administration of FSH [21, 28], and 3) in vivo cessation of follicle growth when FSH levels are depressed by administration of follicular fluid [37]. Various intrafollicular growth factors can influence the effects of FSH [38], but this aspect of folliculogenesis is not covered in this review. Intraovarian relationships occur between successive dominant follicles and the corpus luteum [39], but study is needed on the local relationships among follicles during deviation.

Factors controlling increasing and decreasing concentrations of circulating FSH during an FSH surge have not been defined. The proteinaceous components of follicular fluid, which include inhibin, had a striking inhibitory effect on FSH and follicle growth when administered to cattle [37, 40], and inhibin antiserum increased the circulating FSH concentrations [41]. The follicle-suppressing effect of injected follicular fluid was negated when FSH was also given [42, 43]. Thus, a negative feedback effect of inhibin or other proteinaceous factors potentially play a role in regulating the declining portion of the FSH surge. Inhibin has been measured in growing and atretic follicles of different diameters and at different reproductive stages [44–46]. However, the results are complex and difficult to interpret in the context of this review, resulting primarily from the subunit make-up of inhibin and the wide array of forms with different molecular weights [46, 47]. Furthermore, the time of secretion of inhibin into the circulation relative to the declining portion of the FSH surge is not known. For these reasons, no attempt has been made to incorporate inhibin into the model.

The initial decline in FSH concentrations after the peak of the FSH surge occurs when the future dominant follicle and its largest companions are approximately 6 mm. Aromatase, an enzyme in the estradiol synthetic pathway, is present in 4-mm follicles [48], and low levels of estradiol are present in 5– to 7-mm follicles [49]. It is not known whether estradiol enters the circulation in concentrations that would have a negative-feedback effect on FSH during the initial decline after the peak of the FSH surge. Large doses of exogenous estrogens can suppress FSH secretion under certain conditions [50, 51], but experiments are needed on the effects of physiologic concentrations of estradiol in combination with endogenous inhibin on the FSH surge. The production of small quantities of estradiol by the growing follicles before deviation is depicted in the model by the green lines between follicle stages. Both the systemic and cellular portions of the model depict a possible negative effect of the growing follicles or estradiol on FSH concentrations. The question mark above the minus sign emphasizes that this aspect of the model needs experimental consideration. A recent report [15] suggested that FSH surges may represent the modification of an inherent rhythm; surges occurred in a pregnant heifer at a mean of every 5.5 days over a period of 3 mo without the development of follicles > 5 mm.

NATURE OF THE DEVIATION MECHANISM

Apparently, the final suppression of the FSH surge is a function of the mechanism that causes deviation in growth rates between the resulting dominant and subordinate follicles. The dominant follicle continues to grow and thrive by a shift in primary gonadotropin dependency from FSH to LH, whereas the FSH-dependent subordinate follicles are deprived of FSH. The two postulated aspects of the deviation mechanism are depicted in the model, and the supporting literature is cited below.

A. The Selected Follicle Suppresses FSH, Resulting in Loss of Subordinate Follicles

This aspect of the deviation mechanism involves a final decline in the FSH surge and maintenance of FSH at basal levels, which assures the loss of FSH needed by the subordinate follicles and delays the time of arrival of the next follicular wave. The FSH increase beginning the next surge may be attributed to loss of the effect of inhibitory substances from the extant dominant follicle. The dominant follicle also may secrete factors that directly inhibit other follicles or destroy FSH-deprived, arrested follicles. This possibility is based on the inhibition of follicular growth by injection of follicular fluid without altering circulating FSH concentrations when the fluid was free of inhibin [52] or the fluid was given along with an inhibin antiserum [53]. In addition, injection of the proteinaceous fraction of follicular fluid 3–6 days after ovulation did not depress FSH concentrations below basal levels [23], but did prevent growth of the dominant follicle beyond a mean maximum of 10 mm compared to 14 mm in controls [37]. These studies suggest the presence of an alternative or auxiliary mechanism, but this possibility has not been included in the model pending further experimental support. The principle that a follicle exerts a negative effect on circulating FSH concentrations when it approaches a diameter approximating that of a selected dominant follicle at the time of deviation is supported by the following:

1. Normalization of FSH concentrations to the day of deviation of follicles indicated that, on average, the FSH surge reached basal levels on the day at the beginning of deviation (Fig. 2). Levels of FSH remained low for the next 3 or 4 days until the increase associated with the next surge. By that time, the FSH-deprived subordinate follicles would be unable to respond to the new surge.
2. Removal of the dominant follicle 3 days after ovulation [28] resulted in an immediate surge in FSH [23]. Subordinate follicles were able to respond to the FSH surge when the dominant follicle was removed 3 days after ovulation, but not if removed at 5 days [28]. Similarly, the subordinate follicles at 5 days postovulation did not respond to exogenous FSH [26].
3. Delaying the FSH decline by injecting FSH for 2 days, beginning when the largest follicle was 6 mm, delayed deviation for approximately 2 days [26].
4. Follicles experimentally arrested at 7–9 mm did not suppress FSH [30].
5. Suppression of FSH in pregnant heifers was greater and longer when the associated follicular wave had a largest follicle of $\geq$ 10 mm than when the largest follicle was 6–9 mm [15]. The prolonged and more exaggerated decline in the FSH surge for the $\geq$ 10-mm group was associated with a longer interwave interval (7.4 vs. 5.9 days), interpeak interval (7.1 vs. 5.5 days), and peak-to-nadir interval (3.4 vs. 2.5 days).

B. The Selected Follicle Acquires LH Dependency

The second postulated aspect of the deviation mechanism is a change in emphasis of gonadotropin dependency in the selected dominant follicle so that its continued development is driven by circulating LH. Most perplexing is the presence of the deviation mechanism in follicular waves that occur during a wide array of hormonal environments, especially those involving divergent systemic concentrations and pulse frequencies of LH and progesterone during the estrous cycle and pregnancy. Progesterone and LH are involved in the attained diameter, maintenance, and turnover of the dominant follicle [54–58], but this aspect of folliculogenesis is outside of the focus area of this minireview. The role of LH in follicle deviation and in initial growth of the selected follicle has received only minimal research consideration. Pending clarification, therefore, it will be assumed that transition to LH dependency by the selected follicle occurs even under basal LH concentrations. Therefore, LH is depicted in the model by a band of constant width, without regard to fluctuating mean concentrations or pulse frequencies. Experimental results that support or are consistent with the involvement of LH in the deviation mechanism are the following:

1. In two recent studies [59, 60], granulosa cells acquired LH receptors between Days 2 and 4 after wave emergence or ovulation. Neither study considered Day 3, which is critical according to the model, but Days 2 and 4 do bracket the expected mean day of deviation.
2. Chronic treatment of cattle with a GnRH agonist suppressed the pulsatile secretion of LH, and the largest follicle did not grow beyond 7–9 mm, indicating the necessity of LH for post-deviation development [30].
3. Lactating cows on a low-energy diet [61] had a lower LH pulse frequency, and the diameter of the largest follicle (8.7 mm) was less than in cows on a 100% energy diet (10.2 mm).
4. After the 90th day of pregnancy, there was a transitional decrease in the maximum diameter of the largest follicle of successive follicular waves [15] and a decrease in LH pulse frequency and mean LH concentrations [62], indicating an apparent temporal relationship between maximum follicle diameters and LH concentrations.
5. The life span of the dominant follicle can be extended by increasing LH pulse frequency [54, 55]. Although these and similar findings are from experiments that did not involve deviation between the two largest follicles, they do indicate a functional relationship between the dominant follicle and LH.

The identities of follicular inhibitory substances responsible for the final and continued depression of circulating FSH concentrations and the potential follicular facilitory substances involved in the change in gonadotropin dependency to LH have not been clarified. The dominant follicle produces and releases estradiol at the approximate time of deviation and throughout its subsequent growing phase; therefore, estradiol could be involved in both aspects of the deviation mechanism. Follicular-fluid estradiol concentrations in the largest follicle were elevated when its mean diameter was 8 mm [44], 8.5 mm (2 days after ovulation [59] or 3 days after estrus [47]), or 9 mm [45]. Pulsatile secretion and mean plasma concentrations of estradiol were greater at a mean of 2.5 days postovulation than at a mean of 5.6 days, and the estradiol pulses were associated with LH pulses [24]. In a study involving cannulation of ovarian veins [63], an increase in plasma estradiol occurred from a single ovary, and the high levels were sustained between 3 and 7 days after the LH surge. These findings are consistent with the postulate that estradiol is secreted by the selected follicle near the time of deviation, considering that the mean day at the beginning of deviation in follicle diameters was Day 2.8, when the largest follicle was 8.5 mm. Therefore, estradiol is a candidate for a role in the final and continued systemic depression of FSH and in intrafollicular facilitation of LH dependency. However, this conclusion will remain tentative until the temporal and functional relationships between estradiol production and follicle devi-

ation are verified directly. The greater estradiol production in the dominant follicle after deviation than in all growing follicles before deviation is represented by the green band between the symbols for follicles, and the changing width of the band for the dominant follicle is based on our interpretation of reported circulating estradiol concentrations [24, 63–65].

CELLULAR ASPECTS OF THE DEVIATION MECHANISM

This section should be read with reference to the cellular portion of the model (Fig. 1). The two-cell/two-gonadotropin theory of follicular steroidogenesis is well supported in cattle. Androgens are produced in thecal cells by the 17α-hydroxylase and $C_{17,20}$-lyase activity of the $P450_{c17}$ enzyme. Because thecal cells from early antral, large dominant, and even some atretic follicles contain mRNA for $P450_{c17}$ [66], thecal $P450_{c17}$ expression may not be the primary determinant of deviation. In this regard, of course, provision of sufficient androgen substrate is essential for estrogen production. However, during follicle deviation it is likely that the rate-limiting step in estrogen production is aromatase enzyme. Aromatase mRNA and enzyme activity are first expressed in granulosa cells of growing 4-mm follicles and greatly increase when the growing follicles reach ≥ 8 mm [48, 65]; as discussed above, deviation occurs at 8–9 mm.

Follicular steroidogenesis is regulated by binding of FSH and LH to specific, high-affinity, G-protein-coupled plasma membrane receptors. The role of cAMP in cellular mediation of FSH and LH action is emphasized in the cellular portion of the model; however, other cellular effector systems could also be involved. Receptors for FSH are present on granulosa cells, but not thecal cells, with FSH receptor mRNA expressed in follicles with as few as two layers of granulosa cells [67]. Particularly important in follicle deviation is a dramatic induction of LH receptor mRNA and binding of LH in granulosa and thecal cells of dominant follicles between Days 2 and 4 [3, 59, 60]. In addition, LH-stimulated cAMP production was found primarily in granulosa cells from nonapoptotic, estrogen-active follicles > 8 mm [68]. Thus, the key cellular mechanisms of follicular deviation probably involve alterations in expression of aromatase and LH receptors in granulosa cells and potentially LH receptors in thecal cells when the future dominant follicle reaches 8–9 mm (mean time of deviation).

The physiologic mechanisms involved in cellular differentiation within the selected follicle remain speculative despite extensive work with cultured follicular cells. Many aspects of follicular cell differentiation are probably mediated by local peptides, such as growth factors and their binding proteins [38, 49], and by systemic metabolic hormones, such as growth hormone and insulin [69]. For example, a recent review [70] summarizes the complexity of the ovarian-insulin/insulin-like growth factor (IGF) system, demonstrating the potential autocrine and paracrine actions of IGF-I and particularly its binding proteins during follicle development and atresia. Perhaps, therefore, these growth factors play a key role in the acquisition and maintenance of functional dominance. However, this brief discussion emphasizes the cellular mechanisms involved only in FSH and LH responsiveness, providing continuity between the systemic and cellular gonadotropic mechanisms of the model.

At the expected time of follicle deviation, the number of FSH receptors in granulosa cells did not change in the dominant follicle, but the number of LH receptors increased [59, 60]. Thus, the first follicle to reach a decisive stage at which granulosa-cell LH receptors are expressed may be the follicle that becomes dominant. Speculatively, the acquisition of LH receptors and the resulting LH stimulation may be decisive in the following ways: 1) by stimulating an abrupt increase in estradiol production, which would suppress circulating FSH concentrations, and 2) by increasing intracellular cAMP, which would protect the selected follicle from the FSH decrease. In contrast, the subordinate follicles would be subjected to an intracellular decline in FSH-stimulated cAMP, thereby preventing them from reaching the decisive stage.

Follicular estradiol production during follicle deviation is dependent upon expression of granulosa-cell aromatase activity and androgen substrate from thecal cells. The aromatase enzyme can be acutely regulated at the transcriptional level. The 5′-flanking region of the rat aromatase gene contains a cAMP regulatory element (CRE)-like sequence that, upon binding of CRE binding protein, results in increased aromatase gene expression [71]. In addition, a promoter region of the gene can bind the steroidogenic tissue-specific factor, SF-1 [71, 72]. The SF-1 binding region and cAMP-stimulated SF-1 protein production both appear to be necessary for cAMP-responsive transcription of the human aromatase gene [72]. However, SF-1 and CRE binding protein are present in cell types (human thecal, bovine luteal) that do not normally express aromatase, suggesting that other cell-specific transcription factors restrict aromatase expression to granulosa cells [72]. Thus, granulosa cell aromatase gene expression is regulated, at least in part, by classical CRE-mediated mechanisms, probably stimulated by FSH/cAMP during initial growth of the follicular wave, with a further increase stimulated by LH/cAMP in the selected follicle at deviation.

Because cattle are monovular, it is particularly critical that follicle deviation occur in an expeditious fashion to prevent multiple dominant follicles. Rapid, synchronous expression of LH receptors in granulosa cells and possibly thecal cells of the future dominant follicle may be a pivotal event in the follicle deviation process [60]. The regulatory regions of the bovine LH receptor gene have not yet been analyzed, but these regions have been extensively evaluated in other species. Both FSH and estradiol may be required for expression of the rat LH receptor gene [73], although results in hypophysectomized rats are not consistent with an obligatory requirement for estradiol [74]. Transcriptional activity of the rat LH receptor gene is regulated by complex interactions between multiple regulatory regions with no clearly defined CRE [75, 76]. In bovine follicles, LH receptor mRNA is found in thecal cells of early antral, large, and even atretic follicles, but is found in granulosa cells of dominant follicles on Day 4 but not on Day 2 after emergence [60]. This cell-specific expression pattern and the complexity in transcriptional regulation are consistent with potentially distinct mechanisms regulating LH receptor expression in different cell types and states of cellular differentiation. Resolution of the intercellular and intracellular mechanisms regulating physiologic expression of LH receptors at follicle deviation will provide a key piece in the follicle-selection puzzle.

CONCLUSIONS

Through the contributions of many laboratories, certain aspects of the long-time mystery involving selection of an

ovulatory follicle have been elucidated, and others are approaching resolution. The stimulation of emergence of a follicular wave by a surge in FSH is well established, but the mechanisms for regulating the declining portion of the FSH surge are not. Inhibin and estradiol may be involved, but it is not clear whether adequate concentrations of these hormones are present in the circulation to account for the initial declining portion of the surge. Final suppression of the FSH surge is a function of the deviation mechanism, and the growing dominant follicle maintains the basal concentrations of FSH between surges. Deprivation of the subordinate follicles through basal levels of circulating FSH also is well supported. Evidence is mounting that, despite the suppression of FSH, the selected follicle is able to thrive and grow through a shift in primary gonadotropin dependency from FSH to LH. The resulting cellular LH-driven mechanism supports the dominant follicle throughout its post-deviation growth phase.

The model presented here for the nature of the deviation mechanism in cattle is used in our laboratories to develop hypotheses and design experimental tests. It has served its purpose well and has been the rallying point for our discussions. Hopefully, others also will find it useful. We realize that bad models fade away and good models are revised.

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