The discussion in perspective

R.B. Land

A.R.C. Animal Breeding Research Organisation, West Mains Road, Edinburgh EH9 3JQ, U.K.

The appreciation and respect of the audience for a series of papers which were all very clearly presented and which complemented one another very well was evident throughout. The direction of the discussion tended to reverse the order of presentation and started with the control of seasonal variation in sheep. Cumming pointed out that there was more to seasonality than a sudden change in sensitivity to negative feedback of oestrogen on LH secretion as had been deduced from the rapid changes in LH concentration seen at the beginning and end of anoestrus in ovarioctomized ewes implanted with oestrogen. The progressive build-up in the rate of ovulation towards the middle of the breeding season and its subsequent decline, routinely observed in Australia, suggested another dimension, possibly involving FSH. Cumming also drew attention to the time lags involved and observed that one really had to think in terms of long- and short-term effects. Lamming suggested that the control of seasonal breeding might not be quite as simple or as general as the study of sheep of one breed in one environment might imply. He acknowledged that the long-term ovarioctomized ewe used by his group was not an appropriate model to study seasonal changes in sensitivity to negative feedback but wondered whether the Karsch models were adequate in terms of positive feedback. He asked if oestrogen given shortly after the regression of the last corpus luteum of the breeding season would lead to ovulation (inferring that exogenous administration would overcome the inadequate build up of pre-ovulatory oestrogen due to inadequate LH) but this had not been tried. Secondly, why do sheep ovulate following the withdrawal of progestagen sponges during anoestrus? LH must then be able to overcome negative feedback and stimulate oestrogen production to a sufficient extent to lead to positive feedback and ovulation. Karsch suggested that this may be a characteristic of the progestagen, the dose used, or the stage of anoestrus; in Michigan, when they had used implants to raise physiological levels of progesterone, their removal did not lead to similar events. Reference was then made to the 3 sheep of the 7 infused with LH during anoestrus that did not secrete enough oestrogen to trigger positive feedback. Did this imply a seasonal decline in sensitivity to positive feedback? It was, however, pointed out that the concentrations of oestrogen achieved in peripheral plasma in 2 of these 3 ewes was particularly low, possibly due to a carry-over effect of depression by severe negative feedback before the start of the infusion. Baird commented that high concentrations of LH are known to terminate oestrogen secretion and that the infusion of 4 ng LH/min could have been on the borderline since 3 ng/min stimulated and 5 ng/min terminated oestrogen secretion. (The 3 ewes which failed to ovulate may, however, give us as much information as the 4 which did.) The role of variation in positive feedback in anoestrus was also discussed earlier in the meeting when Friman and others reported that they, like Karsch, could not detect seasonal differences. Cumming stated that he and his colleagues have found photoperiodic effects on positive feedback in support of the original observation of seasonal differences made by workers at A.B.R.O. The balance between the dose of oestrogen and the seasonal characteristics of the breed studied were agreed to be relevant; the Suffolk sheep used in Michigan would, for example, ovulate in response to stress at any time of anoestrus; the Finnish Landrace in the original study of Land and his colleagues at A.B.R.O. have been postulated to be particularly insensitive to oestrogen. There are two separate
questions, "does a seasonal decline in sensitivity to positive feedback contribute to the cessation of oestrous cycles?" (to which the Karsch data say no) and secondly, "might such variation nevertheless exist and contribute to our understanding of the basic changes in hypothalamic activity throughout the year?" (to which Karsch has not yet addressed himself and to which the answer might well be yes). Cumming pointed out that the first ovulation at the beginning of the breeding season is not preceded by increased progesterone. This can be extrapolated to suggest that, although failure of positive feedback may not precipitate the end of one breeding season, it may delay the onset of the next.

The postulated prolactin sensitization of steroid feedback on gonadotrophin release (by McNeilly) and the known higher concentrations of prolactin during anoestrus in the sheep, led to a request from Short for comments in turn from Karsch, Ben-Jonathan and Domanski. Although the studies of Karsch did not preclude a contribution by prolactin, he pointed out that a dissociation of periodic variation in prolactin and the occurrence of oestrous cycles had been reported from Nouzilly, which suggested their independence. An exhibit at the current meeting (by Howles and Haynes) demonstrated seasonal variation in testis function to be independent of prolactin titre when rams were kept on a constant long photoperiod and to occur in association with persistent low prolactin concentrations when rams were kept on a constant short photoperiod. Ben-Jonathan commented that little is known about the rate of dopamine turnover in the sheep, but from studies in rats it appears that males were particularly sensitive to inhibition of prolactin secretion by dopamine. Domanski supported McNeilly's concept that dopamine turnover had to be reduced if the secretion of LH were to increase and referred to his observation of a marked prolactin peak before the preovulatory discharge of LH; noradrenaline stimulates LH release, dopamine inhibits noradrenaline, therefore dopamine has to drop to allow noradrenaline to act and prolactin inevitably rises. Neither McNeilly nor G. Lincoln wished to take up the dissociation of prolactin and seasonality and Lincoln returned to the question of basic changes in LH secretion during the year; Lamming felt that studies of the sheep and rat had led to too much emphasis on prolactin.

What is the link between changes in daylength and changes in sensitivity to steroid negative feedback? Lincoln has shown that in the Soay ram there is a progressive change during the year in the circulating levels of LH and FSH; the values are lowest in spring and highest in late summer and autumn. These seasonal changes are apparently dictated by changes in LH-RH secretion by the neurones of the median eminence (principally a change in the frequency of episodic secretion). The crucial question is whether the changes in hypothalamic activity result from an alteration in the sensitivity to the circulating steroids, as suggested by Karsch, or from changes in the CNS influenced by photoperiod which themselves regulate the release of LH-RH. In this case, the apparent change in sensitivity to negative feedback is the result of changes in the "drive" from the hypothalamus. In support of this latter suggestion are the observations made on a variety of seasonal variations in gonadotrophin secretion that occur in castrated animals in which the effects of sex steroid are lacking. Karsch replied that their, and particularly his colleague Goodman's, current hypothesis was that during the breeding season oestrogen acted at the level of the pituitary gland to control (i.e. reduce) the amplitude of LH pulses, whereas during anoestrus it acted at the level of the brain as well. In this way oestradiol would gain the ability to reduce LH pulse frequency by decreasing the frequency of LH-RH release. (Steroid independent changes in hypothalamic activity would thus seem to be implied.)

Chang wondered how the control of seasonality in other animals compared with that in sheep and the chairman invited Concannon to consider the relevance of the sheep data and the hypotheses developed from these data to seasonal variation in reproduction in mink. Sufficient results from this species were not available, largely because assays were not yet adequate. Attention returned to sheep as Foxcroft suggested the real "block" was a "steroid block"; could a rebound effect be demonstrated with antioestrogens? Answers were not volunteered. Oldham suggested that the introduction of the ram (which induces a sudden and marked increase in the
frequency of LH pulses in the ewe) might give a better model to study positive feedback during anoestrus than infusions into ewes. Cunningham asked what happened if the suprachiasmatic nuclei were stimulated rather than destroyed; would sheep then cease to show oestrous cycles? Unfortunately Domanski did not have an appropriate system for stimulation, and had not been able to conduct the experiment.

As the discussion drew to a close, Chang stimulated McKnight to comment that β-endorphin was thought to induce euphoria, and certainly did so as a subject for investigation. Cook then pointed out the general euphoria following an excellent symposium (for which he himself deserves much of the credit) and drew it to a close. The symposium pulled together studies on hypothalamic anatomy, the roles of catecholamines and of opioid-like peptides, and the interaction of prolactin and steroids with gonadotrophin release. Hopefully, it would stimulate further experiments leading to a greater understanding so that it will be unnecessary to use vague terms such as ‘hypothalamic activity’, and ‘sensitivity to negative feedback’ may become more than a concept. Finally, Karsch said that some of his studies had been stimulated by a question raised when he presented a report of his earlier work at the University of Nottingham Easter School. The next question may well be “Do sheep start to cycle for reasons opposite those that cause them to stop?".