THE RELATIONSHIP BETWEEN LACTATION AND THE RELEASE OF PROLACTIN AND GROWTH HORMONE IN THE GOAT

I. C. HART

*National Institute for Research in Dairying,
Shinfield, Reading RG2 9AT*

The ability of pituitary hormones to cause udder growth and to initiate milk secretion in the goat was clearly demonstrated when it was shown that both mammary growth and lactation were induced in the ovariectomized virgin goat by twice-daily application of the milking stimulus (Cowie, Knaggs, Tindal & Turvey, 1968). It was further demonstrated that both of these responses were completely abolished in animals in which the pituitary stalk was transected before 'milking' was started. As earlier work had shown that suckling often resulted in a fall in pituitary hormone concentration (see Cowie & Tindal, 1971) it seemed probable that both mammary growth and lactation were initiated by elevated blood levels of pituitary hormones. Concerning the maintenance of milk secretion, partly successful hormonal replacement studies in the hypophysectomized lactating goat were first described by Cowie & Tindal (1961) followed by Gale & Larson (1963). Complete restoration and maintenance of the milk yield was subsequently achieved with a combination of ovine prolactin, bovine GH, tri-iodothyronine, protamine zinc insulin and dexamethasone (Cowie, Knaggs & Tindal, 1964). The presence of prolactin was important for the restoration of the milk yield to the pre-hypophysectomy level but it was not always necessary for the maintenance of lactation at that level (Cowie, 1969).

The anterior pituitary hormones prolactin and GH would thus appear to play an essential rôle in the establishment and maintenance of lactation in the goat. Using radioimmunoassays for ovine/caprine prolactin (Hart, 1972a, 1973b) and caprine GH (I. C. Hart, D. S. Flux, P. Andrews & A. S. McNeilly, in preparation), it has now been possible to measure the circulating levels of these hormones under a variety of conditions in the goat and thereby attempt to determine whether or not a temporal relationship exists between the circulating concentrations of the hormones and the level of milk production. Plasma samples were obtained from pedigree British Saanen goats, each goat being housed singly in a stall and maintained on a diet of concentrates and hay. To minimize disturbance and to obtain serial samples of blood readily, an indwelling polyethylene cannula (Sterivac size 4, Allen & Hanbury Ltd) was inserted into one of the external jugular veins (Folley & Knaggs, 1965) not less than 15 hr before the first sample was taken.

PROLACTIN DURING PREGNANCY AND PARTURITION

The blood level of prolactin in five pregnant goats rose between 5 and 37 hr

before parturition (Text-fig. 1), finally reaching a concentration which was 2.6 to 4.5 times higher than the lowest concentration of prolactin found earlier in gestation (Hart, 1972a). A much smaller increase was found in one animal (Goat 281; Text-fig. 1), in which also the peak concentration (224 ng/ml) was reached earlier (-27 hr) than in the other goats, decreasing to 106 ng/ml at

TEXT-FIG. 1. Concentrations of prolactin in the jugular blood of five pregnant goats before parturition. (From Hart, 1972a.)

-6 hr. These findings are in agreement with those of Johke, Fuse & Oshima (1971) and Buttle, Forsyth & Knaggs (1972) for the goat, a similar rise in the concentration of prolactin having also been found at this time in several other mammals (rat—Amenomori, Chen & Meites, 1970; cow—Schams & Karg, 1969; sheep—Davis, Reichert & Niswender, 1971). The levels of prolactin in

TEXT-FIG. 2. Levels of prolactin in the jugular blood of Goat 370 during parturition. MUC = mild uterine contractions; IUC = intense uterine contractions; VD = vaginal discharge; HF = head and feet visible; H = head presented. (From Hart, 1972a.)

man, however, differ from those found in other mammals in that there is a gradual increase in the concentration of prolactin throughout the last half of pregnancy until parturition occurs (Berle & Apostolakis, 1969; Hwang, Guyda & Friesen, 1971; L'Hermite, Stavric & Robyn, 1972). It has been postulated that higher circulating levels of oestrogen might account for this increased prolactin in pregnant women (Hwang *et al.*, 1971).

The concentration of prolactin measured in the blood of one of eight goats serially sampled during parturition is illustrated in Text-fig. 2. In all the goats the circulating level of prolactin remained high during parturition, significant increases being found only in response to specific stimuli, e.g. the onset of mild

TEXT-FIG. 3. Oxytocin (○) and prolactin (●) concentrations in jugular vein blood taken from one goat during second stage labour. Expulsion indicates the birth of a kid.

or intense uterine contractions or the expulsion of a first or second kid. Stress has been shown to be a potent stimulus for prolactin release in the goat (Johke, 1970; Bryant, Linzell & Greenwood, 1970; Hart, 1973b); it seems likely, therefore, that the increases in plasma prolactin concentration during parturition were due to stress, possibly associated with the distension of the cervix and vagina during delivery.

The measurement of prolactin levels in blood collected throughout parturition presented an ideal opportunity to test, in a physiological situation, the validity of the hypothesis that in certain circumstances oxytocin may stimulate the release of prolactin from the anterior pituitary (Benson & Folley, 1956). The plasma levels of oxytocin in samples taken during parturition from six goats were determined by Dr A. S. McNeilly (Department of Chemical Pathology, St Bartholomew's Hospital, London, E.C.1) using the method of Chard, Boyd, Forsling, McNeilly & Landon (1970). The results for one of the goats are given in Text-fig. 3; similar results were obtained for the other five animals. Despite extremely large increases in the concentration of oxytocin (2 to 745 pg/ml), the increases in the circulating level of prolactin were relatively small in comparison with the magnitude of the release that usually occurs at milking (Bryant, Greenwood & Linzell, 1968; Johke, 1969; Hart, 1972b) when the quantity of oxytocin released is often less than that released during parturition (Folley & Knaggs, 1965; McNeilly, 1972). The results suggest, therefore, that during labour oxytocin plays no part in prolactin release.

BASAL CIRCULATING LEVELS OF PROLACTIN

Measurement of basal levels of prolactin in the ruminant have been restricted to the cow, somewhat contradictory findings having been published, especially with respect to the existence of a circadian rhythm. No circadian variation was found by Schams & Karg (1970) who reported marked fluctuations in blood prolactin throughout 20 hr of the day. Although subsequent authors have claimed a circadian pattern of hormone release in the cow (Swanson & Hafs, 1971; Koprowski, Tucker & Convey, 1972), they vary in their assessment of when maximum concentrations of prolactin occur. Furthermore, in the study of Swanson & Hafs (1971), the range over which the concentration of prolactin fluctuated was very small (approximately 10 to 17 ng/ml), no indication of statistical significance being given. Possible explanations for these discrepancies might be that different sampling times (30 min to 3 hr) were employed by different investigators and that little attention was paid to the season of the year.

There is no evidence of a circadian pattern of prolactin release in the virgin female or castrated male goat (Text-figs 4b and 4c; Hart, 1973b). The average levels determined in blood samples taken at 30 min intervals throughout a single 24 hr period were higher in four castrated males than those measured in four virgin females. The castrated male goats also showed greater variation in prolactin concentrations both between goats and between samples from the same goat. Although, in certain circumstances, feeding is said to elevate blood prolactin in the cow (Johke, 1970; Schams & Karg, 1970; McAtee & Trenkle, 1971) and the goat (Bryant *et al.*, 1970), no obvious relationship was observed in

these animals between the level of hormones and the feeding of concentrates (Text-figs 4a, b and c); the goats did, however, have constant access to hay.

A distinct circadian release of prolactin, synchronized by morning and afternoon milking, was found in four lactating female goats (Text-fig. 4a). The results further indicated that the stimulus of morning milking, as well as causing an immediate release of prolactin, may also initiate a gradually

TEXT-FIG. 4. Average basal levels of prolactin ($\pm$ S.E.M.) found in blood samples taken at 30-min intervals from four anoestrous lactating female (A: 9 August 1971), three castrated male (B, 13 July 1971) and four anoestrous virgin female (C: 26 July 1971) goats throughout a 24-hr period. H = high value due to one abnormally high result.

decreasing chronic release of the hormone, continuing until afternoon milking when the process is repeated. Although the significance of high circulating levels of prolactin is still not clear (see Discussion), such a mechanism ensures that the mammary gland of the lactating goat is, for 14 to 16 hr of the day, exposed to higher levels of prolactin than those occurring in virgin female, castrated male or lactating female goats that have not been exposed to the milking stimulus for 7 to 9 hr.

These results, however, must be interpreted only in the context of the time of year in which the samples were taken (Text-figs 4a, b and c), as recent work has indicated that the basal level of prolactin in lactating cows and heifers and in one bull may be related to the season of the year (Schams, 1972). My observation (Hart, 1973c) that prolactin levels in control blood samples taken before milking are significantly higher earlier in the year (March to September) than in October and November supports the existence of a similar seasonal effect in the goat.

RELEASE OF PROLACTIN AND GH AT MILKING

The development of radioimmunoassay techniques for the measurement of prolactin in a number of species has enabled workers to confirm that the suckling/milking stimulus often results in an increased concentration of the hormone in the blood (goat—Bryant *et al.*, 1968; rat—Kwa & Verhofstad, 1968; cow—Johke, 1969; sheep—Fell, Beck, Brown, Cumming & Goding, 1972; woman—Hwang *et al.*, 1971). Bioassay of pituitary GH in the rat suggests that this hormone too may be released by suckling (Grosvenor, 1964; Grosvenor, Krulich & McCann, 1968; Tucker & Thatcher, 1968; Sar & Meites, 1969) but this finding remains to be confirmed by radioimmunoassay studies. As milk secretion cannot long continue, in any mammal, in the absence of the regular removal of milk from the mammary gland, the relationship between the maintenance of lactation and the release of prolactin at suckling has been the subject of considerable investigation in monogastric animals. For the rat, at least, it has been shown that the release of prolactin at suckling is essential for continued milk production (Shaar & Clemens, 1972) and that milk production is probably related to the quantity of prolactin released (Kruulich, Kuhn, Illner & McCann, 1970). Similar results have been obtained in women (Besser, Parke, Edwards, Forsyth & McNeilly, 1972; Varga, Lutterbeck, Pryor, Wenner & Erb, 1972).

The possible significance, in terms of milk production, of the concentrations of prolactin and GH present in the blood at milking was investigated in six goats by taking serial blood samples at a milking once a month throughout a complete lactation cycle (April to November, 1971), samples being collected at intervals of 30 sec to 1 min for up to 36 min after the start of milking. The plasma obtained from each of the samples was assayed for prolactin. Plasma samples obtained at milking early (April and May) and late (October and November) in lactation were also assayed for GH.

A large increase in the concentration of circulating prolactin at milking occurred in all six animals for the months between April and September, the level of prolactin in the blood increasing within 1 to 2 min of the application of the milking stimulus and reaching a peak after 2 to 15 min. Although there was usually an increase in the level of prolactin in blood samples taken at milking in October and November, the average quantity of hormone released by the goats at this time was significantly lower ($P < 0.001$) than that found between April and September. There was a correlation between the average quantity of prolactin released each month at milking (April to November) and the average milk yield of the six goats ($r = 0.67$; $P > 0.05$), but in view of

the results obtained using the drug 2-Br- α -ergocryptine (p. 492) the physiological significance of this is uncertain.

No correlation was noted between the duration of milking and the quantity of prolactin released into the circulation ($r = -0.24$; $P > 0.1$), or between the average quantity of prolactin found at milking (April to August) and the average milk yield of the individual goats ($r = -0.57$; $P > 0.1$). No evidence for a conditioned release of prolactin was obtained in samples taken before milking in June.

TEXT-FIG. 5. Levels of growth hormone found at milking in six goats during early and late lactation. $\circ$, Goat 464; $\bullet$, Goat 447; $\triangle$, Goat 430; $\blacktriangle$, Goat 435; $\square$, Goat 452; $\blacksquare$, Goat 410. The distance between the vertical broken lines indicates average milking time. (From Hart & Flux, 1973.)

A large increase in the circulating level of GH was detected in eight of the twelve series of blood samples taken at milking during early and late lactation (Text-fig. 5; Hart & Flux, 1973). The rise in GH concentration differed in several characteristics from that in prolactin: there was a longer delay (2 to 7 min) between the start of milking and a rise in the level of GH; when increases in the concentration of GH and prolactin occurred in the same series of blood samples, the levels rose independently, the peak concentration of GH occurring

over a wider range (4 to 36 min) than that of prolactin (Text-fig. 6). These limited results showed no correlation between the average quantity of GH released at milking and the average weekly milk yield of the six goats.

Analysis of serial blood samples taken at milking from the same six goats on Days 2, 7 and 12 of lactation indicated that no correlation exists between the average quantity of prolactin released at milking and the gradually increasing milk yield at this time ($r = 0.36$; $P > 0.1$).

EFFECT OF 2-BROMO- α -ERGOCRYPTINE ON MILK YIELD AND THE LEVEL OF PROLACTIN AND GROWTH HORMONE IN THE BLOOD OF THE GOAT AT MILKING

In view of the results obtained from the experiments outlined above, it was deemed of interest to investigate the effect of 2-Br- α -ergocryptine methane

TEXT-FIG. 6. Concentrations of prolactin (○) and GH (●) found in the same serial blood samples taken from Goat 357 before, during and after milking. C = control blood sample.

sulphonate (= CB-154, kindly supplied by Sandoz Ltd, Basel), a drug known to inhibit the release of prolactin from the anterior pituitary of the rat, on the milk yield and on the release of prolactin and GH at milking in the goat (Hart, 1973a).

Three lactating female goats were injected subcutaneously each day (at approximately 14.00 hours) with 1.5 ml of CB-154 dissolved in a solution of ethanol and 0.9% NaCl solution (40:60, v/v). Administration of the drug was maintained for 44 days over the period 11 July to 22 August 1972. Initially each goat was injected with 5 mg CB-154/day and this dose was increased to 10 mg/day and 20 mg/day on 24 July and 3 August respectively (Text-fig. 7). To control the effect of daily subcutaneous injections on the milk yield, three other goats were injected with 1.5 ml of the vehicle alone. Blood samples were

TEXT-FIG. 7. Milk yield of three control goats (●) and three goats treated with CB-154 (○). S = date of blood sampling. (From Hart, 1973a.)

collected during and after morning milking 5 days before the injection of CB-154 (5 mg/goat/day) was started (S1; Text-fig. 7); 3 days before the dosage was changed to 10 mg/goat/day (S2); 2 days before the dosage was changed to 20 mg/goat/day (S3) and finally 19 days later (S4).

Analysis of the plasma clearly indicated that the administration of only 5 mg CB-154/goat/day effectively blocked the release of prolactin from the anterior pituitary of the goat at morning milking yet allowed the release of GH to occur (Table 1; Text-fig. 8). The concentration of prolactin in blood

Table 1. Average concentrations of prolactin and GH found in serial blood samples taken from three goats during and after milking

Time of blood sampling*	Treatment (mg CB-154/goat/day)	Prolactin (ng/ml)	GH (ng/ml)
S1	0	465.2 ± 57.1	27.4 ± 9.1
S2	5	19.4 ± 3.6	38.9 ± 11.0
S3	10	9.6 ± 1.3	52.9 ± 3.0
S4	20	6.1 ± 0.4	63.9 ± 10.6

Values are means ± S.E.

* Blood samples were taken for 40 min during and after milking at S1, S2, S3 and S4 (see Text-fig. 7).

samples taken just before milking also indicated that CB-154 decreased the usual basal circulating level of prolactin in the lactating female goat and that the fall in the level of prolactin might be related to the dose of CB-154 used (the average pre-milking prolactin concentration for all three goats ± S.E.M. was 38.0 ± 8.9 , 18.5 ± 4.5 , 8.9 ± 1.1 and 5.04 ± 0.03 ng/ml at 0, 5, 10 and 20 mg dose levels of CB-154 respectively).

If the quantity of GH released at milking is expressed as the average concentration of GH found in blood samples taken over 40 min during and after milking, there is an indication that the quantity of GH released by the milking stimulus increased as higher dosages of CB-154 were used. Statistical analysis

TEXT-FIG. 8. Release of GH in response to milking at the times indicated in Text-fig. 7. (a) S1—no CB-154; (b) S2—5 mg CB-154/goat/day; (c) S3—10 mg CB-154/goat/day; (d) S4—20 mg CB-154/goat/day. ●, Goat 486; ○, Goat 496; △, Goat 572.

showed that whilst there was no significant difference ($P > 0.1$) between the quantity of GH released at S1 and S2, a significant difference ($P < 0.02$) existed between the quantity of GH released at S1 and that found at S3 and S4.

Despite the substantial fall in the basal circulating level of prolactin and the complete absence of any increase in the concentration of prolactin at milking, the milk yields of the goats injected with CB-154 remained unchanged in comparison with those of the goats injected with the vehicle alone (Text-fig. 7). The fall in milk yield at the end of July occurred throughout the herd.

STIMULI CAUSING THE RELEASE OF PROLACTIN AND GROWTH HORMONE

It has been suggested that three types of stimulus may cause the release of hormones from the pituitary of ruminants at milking: the tactile stimulus of manipulating the teats; a conditioned stimulus associated with the events which take place just before milking; a metabolic stimulus, possibly caused by the increased uptake of one or more milk precursors by the mammary gland after milking. The following experiments were designed to investigate these possibilities.

Experiment 1. To evaluate the significance of the conditioned stimulus in

causing the rise in the concentration of circulating prolactin and GH at milking, the familiar stimuli associated with milking were removed by taking serial blood samples from four goats milked under cyclopropane-oxygen anaesthesia. In order that each goat should function as its own control, blood sampling was carried out 2 days earlier in the conscious animal under normal milking conditions.

Increases in the circulating level of both prolactin (754 ± 221.4 ng/ml $\pm$ S.E.M.) and GH (25.3 ± 13.1 ng/ml) occurred when the animals were milked under anaesthesia and these did not differ significantly ($P > 0.1$) from the releases obtained at the control milkings (prolactin: 836 ± 96.8 ng/ml; GH: 17.2 ± 7.0 ng/ml).

Experiment 2. Experiments to investigate the significance of tactile stimuli, and the possible existence of a metabolic stimulus, causing the release of prolactin and GH from the anterior pituitary of the goat at milking, have been carried out in collaboration with Dr J. L. Linzell (A.R.C. Institute of Animal Physiology, Babraham, Cambridge) using goats in which half of the udder (i.e. one mammary gland) had been transplanted to the neck. Such transplants have an efficient vascular system, but no nervous connections with the central nervous system (Linzell, 1960, 1963). Serial blood samples (5 ml) were taken from four such goats in which the transplanted gland was milked first, followed after 35 to 40 min by the milking of the remaining intact gland.

A rise in the circulating level of prolactin occurred only in response to the milking of the intact mammary gland; no increase was found after the transplanted gland was milked, thus indicating that prolactin is released only by the tactile stimulus of milking. Contrary to the results for prolactin there was a significant rise in the circulating level of GH at various time intervals (2 to 31 min) after starting to milk the transplanted gland. These levels, moreover, increased further after the intact gland was milked. It is possible that the rise in the blood level of GH, following the removal of milk from the transplanted gland, may have been caused by the mammary gland increasing the rate of uptake of certain milk precursors from the blood, this deficit in circulating metabolites thereby stimulating the secretion of GH from the anterior pituitary. Work is in progress to investigate this hypothesis.

DISCUSSION

The results of the above experiments demonstrate quite clearly that pregnancy and parturition modify the blood concentration of prolactin in the goat and that increases in the circulating levels of both prolactin and GH are induced by the stimulus of milking. The relevance of these hormonal changes in terms of milk production, however, is not so clear. Although it is tempting to assume a relationship between the increased level of prolactin, occurring a few hours before parturition (Text-fig. 1), and the onset of milk secretion, in the absence of any knowledge of the circulating levels of other anterior pituitary hormones in the goat one can only speculate as to the function of prolactin at this time. Various mechanisms have been suggested for the hormonal and enzymatic control of the onset of milk secretion (for reviews see Reynolds & Folley, 1969; Kuhn, 1971; Denamur, 1971; Cowie & Tindal, 1971); the situation is com-

plicated, however, by the fact that the time of the onset of milk secretion varies with the species, thereby suggesting that the mechanism controlling milk secretion may also vary. Secretion containing lactose and fat globules occurs in the alveoli of the goat mammary gland approximately 40 to 65 days before parturition (Cowie, 1971; E. A. Jones, personal communication). In view of the low levels of prolactin found in the goat during pregnancy and the presence of a placental lactogen (Buttle *et al.*, 1972), it seems probable that this early secretion occurs in response to other hormones.

Karg & Schams (1971) milked a cow 6 to 7 days before parturition and obtained a milk yield of 15 to 20 kg/day, but noted that the rise in the level of prolactin still occurred at parturition. Moreover, the milk yield of the cow further increased within 2 days of parturition to 20 to 30 kg/day. The importance of the presence of prolactin for milk secretion in the cow at this time was then more directly demonstrated by reducing the release of prolactin to sub-basal levels (using 2-Br- α -ergocryptine) for a few days before and after parturition, when the milk yield of the animal was reduced by 95% of the yield expected on the basis of the previous year's lactational performance (Schams, Reinhardt & Karg, 1972). In the cow, at least, it seems that the elevated level of prolactin before parturition, and its regular release at milking or suckling after parturition, is concerned in further increasing milk secretion in the already well developed mammary gland.

It has been shown that two non-pregnant goats kept in continuous lactation by twice-daily milking still exhibited marked seasonal changes in the milk yield from one year to the next (Linzell, 1973). No information is available on the prolactin levels in these animals but if an increased concentration of prolactin in the blood is essential to restore a high level of milk production in the goat, as it appears to be in the cow, it seems likely that, in the spring, an increase in prolactin production took place in these constantly milked unmated animals, similar to that normally occurring in postparturient goats. Thus the rise in the circulating level of prolactin and the ability to release large quantities of the hormone at milking may occur in the absence of pregnancy and parturition, possibly as a result of an innate rhythm of prolactin release synchronized by environmental cues. Evidence has in fact been obtained to suggest that seasonal changes in the level of prolactin in the goat are markedly influenced by daylength (Buttle, 1974; I. C. Hart, unpublished work). In the goat, therefore, pregnancy may inhibit early in the year what would otherwise be a spontaneous increase in the ability of the animal to release larger quantities of prolactin.

In view of the inhibitory effect of high concentrations of progesterone on milk secretion in some species, it is interesting to note that the rise in the level of prolactin in the goat follows closely upon the sharp fall in the circulating level of progesterone which occurs 2 to 3 days before parturition (Thorburn & Schneider, 1972). Challis & Linzell (1971) have shown that during pregnancy in the goat the level of total oestrogen increased gradually 80 days before parturition, with a sharp increase just before parturition. There is no direct evidence, in the goat, to show that the administration of oestrogen stimulates prolactin release, but in the cow it has been shown that infusion of oestradiol-17 β

will cause a marked increase in circulating prolactin (Schams & Karg, 1972). It is possible, therefore, that the rise in the level of prolactin before parturition is caused by a fall in progesterone concentration in the presence of high circulating levels of oestrogen.

Despite the fact that the concentration of prolactin in the blood of the lactating goat is, for 14 to 16 hr of the day, maintained at a higher level than that found in non-lactating animals (Text-fig. 4), work in both the cow (Karg, Schams & Reinhardt, 1972) and the goat (Text-fig. 7; Hart, 1973a), in which blood levels of prolactin were markedly reduced by means of the drug 2-Br- α -ergocryptine, clearly indicates that high circulating levels of prolactin are unnecessary to maintain the milk yield during mid-lactation. These results in ruminants are contrary to those found in some monogastric animals (Shaar & Clemens, 1972; Besser *et al.*, 1972; Varga *et al.*, 1972), but were not entirely unexpected as, once the yield milk has been restored after hypophysectomy in the lactating goat, lactation can be maximally maintained for over 3 weeks using a combination of hormones (bovine GH, tri-iodothyronine and dexamethasone) not including prolactin (Cowie, 1969). It seems likely, therefore, that during mid-lactation the endocrine demands of the lactating mammary gland are met by GH and other hormones; it should not be forgotten, however, that the use of 2-Br- α -ergocryptine does not completely eliminate prolactin from the circulation (Table 1) and that sufficient residual prolactin may have remained to maintain the milk yield in this experiment.

It should also be remembered that significantly larger quantities of GH were released after the use of the drug (Text-fig. 8; Table 1), so that the quantity of GH released at milking may possibly have increased to compensate for the lack of prolactin. In the absence of any information as to how the quantity of GH released at milking in the goat may vary with the stage of lactation or the season of the year, and in view of the fact that the results were obtained from only three goats (one of which did not show a significantly larger release of GH at S4 than at S1; Goat 496, Text-fig. 8), such an hypothesis must be regarded as speculative.

ACKNOWLEDGMENTS

The author wishes to express his thanks to Dr A. T. Cowie, Dr J. S. Tindal and Dr G. S. Knaggs for helpful criticism and discussion and to Mrs P. Sheffield, Mrs K. Danby and Mrs L. Blake for skilled technical assistance. This work was supported by a Scientific Research Council Research Studentship.

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