consequences of the technique exist, either with the cloned animals or their offspring, before it is adopted commercially.

Nuclear transfer relies on a sufficient understanding of the basic reproductive biology and embryology of the species concerned. We are fast approaching this point in deer species. It is therefore timely to consider what new opportunities exist for the deer industry by integrating an efficient cloning method into production systems of the future. Applications exist in the ability to rapidly multiply genetically superior individuals, however, this relies on accurately selecting elite genotypes. Cloning strategies could both increase the rate of genetic gain and the dissemination of this genetic gain from breeding herds to the commercial industry. This could be managed without overly reducing genetic diversity amongst the elite breeding population. Herds of cloned individuals may have more similar performance characteristics, aiding management or production, however, it must be remembered that animal phenotype is an interaction between genotype and the environment. A significant impact of the technology may be in conjunction with gene technology to produced transgenic animals. As understanding of the genes that regulate production traits are better understood in the future, so too will the ability to genetically enhance these by manipulating specific gene sequences in cells growing in the laboratory before nuclear transfer is used to produce animals from these cells. Ultimately, these genetic modifications will be more precise and direct than what can be achieved with conventional breeding. The scientific breakthrough that led to Dolly has opened up a range of potential opportunities for animal industries to embrace.

## NEW DIRECTIONS FOR THE CONTROL OF SEASONAL BREEDING IN RED DEER

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Like their wild counterparts, farmed red deer hinds commence breeding each autumn at a time which means that the earliest dates of calving occur well into summer. In New Zealand pasture production reaches a peak in spring, so the productivity of pasture-based deer farming could be improved if deer were to calve much earlier than they do at present.

Techniques used to advance the onset of seasonal breeding in red deer so far have met with variable and limited success. Depending on the length and timing of treatment, melatonin can advance the mean calving date by up to 5 weeks but since it can cause premature cessation of lactation, the procedure has to be restricted to nulliparous females (Asher *et al.*, 1993a). Likewise, attempts to overcome seasonal anoestrus by administration of gonadotrophins or gonadotrophin-releasing hormone (GnRH) analogues have met with limited success (Duckworth and Barrell, 1988; Fisher and Fennessy, 1985; Moore and Cowie, 1986). We therefore have focussed attention on possible new lines of approach to the long-standing desire to exercise control over the calving season of red deer.

In the last decade it has become clear that the thyroid glands play an important part in the regulation of reproductive seasonality in mammals. Specifically, thyroid hormones are required for the termination of the breeding season. This has been demonstrated in sheep (Nicholls *et al.*, 1988; Moenter *et al.*, 1991) and red deer (Shi and Barrell, 1992, 1994; Anderson and Barrell, 1998 a, b). The role of thyroid hormones appears to be 'permissive', i.e. a small amount of thyroid hormone needs to be present for cessation of reproductive activity (Dahl *et al.*, 1995) but the thyroid glands do not have a regulatory function in this process. Nevertheless, it can be argued from these findings that if the thyroid hormones are removed from the site of action of this mechanism then seasonal reproductive activity in the form of regular ovulatory cycles should persist indefinitely. Thus, females which have commenced ovulating could be held over for mating much later on so that their calves are born in spring, or at any pre-determined date.

Conceptually, this augers well for the development of on-farm procedures to change the calving season of red deer, however there are potential difficulties to be overcome. For instance, removal of thyroid hormones in experimental studies has usually been achieved by surgical removal of the thyroid glands - thyroidectomy. Thyroidectomized animals can be reinstated to normal thyroid status by regular (we use 3 x weekly) injections of thyroid hormones. However, these procedures can not be proposed as serious techniques for application in the deer industry.

An alternative to thyroidectomy is suppression of thyroid hormone secretion by administration of appropriate drugs, e.g. goitrogens. Unfortunately, the chemicals available for this purpose do not appear to be able to achieve the depth of suppression required, can be toxic, and require daily administration. Alternative approaches to this task could include targetted destruction of thyroid tissue by selective toxins or antibodies and control of gene expression in thyroid cells. We have been experimenting with the possibility that exogenous tri-iodothyronine ($T_3$) may be sufficiently potent to suppress endogenous thyroid hormone secretion by negative feedback on the thyroid regulating system at doses insufficient to activate the reproductive switch off mechanism in the brain. Our preliminary studies to trial this approach have been carried out in sheep (Saleh *et al*, 1998) and are ongoing, but have not proven fruitful yet.

There are grounds for optimism. A solid body of evidence is emerging to indicate that the need for presence of thyroid hormones to switch off reproduction is short-lived, i.e. there is a 'window' of time each year when these hormones have to be present (Thrun *et al.*, 1996, 1997). If a temporary, reversible, suppression of thyroid gland secretion can be achieved with a single application of drug, then all requirements for controlling the breeding season in deer may be met. This would also overcome another problem. Continued suppression of thyroid function is effectively hypothyroidism, a situation that interferes with expression of mating behaviour, fertilisation and lactation in red deer. We have found red deer hinds tolerant of thyroidectomy in terms of general health and capable of conceiving, delivering and rearing calves completely out of season whilst thyroidectomized, but the success rate was unacceptably low. Any interruption of thyroid secretion to achieve control of the breeding season in deer will have to depend on temporary suppression of the glands.

It is almost certain that thyroid hormones act on the brain to cause the seasonal onset of reproductive inhibition in mammals (Viguié *et al.*, 1999), but details of the central mechanism are unknown. Nevertheless, this must involve one of the neural pathways which impinge on the GnRH releasing neurons in the hypothalamus and understanding of this could lead to techniques which block thyroid hormones or their actions on the brain, thus avoiding the need for general hypothyroidism. The possible mechanisms by which thyroid hormones might influence reproduction are only beginning to be investigated in the ewe. A recent preliminary finding in this species, namely that there is a thyroid-dependent reduction in the number of axons terminals contacting GnRH cells in the hypothalamus, suggests that thyroid hormones are required for seasonal alterations in inputs to GnRH neurons (Fitzgerald *et al.*, 1999). Other current studies in the ewe are focusing on the site of action of thyroid hormones in the brain, the role of thyroid hormones in mediating the activity of neurons which respond to changes in melatonin secretion (Daveau *et al.*, 1999), and also on the inhibitory dopaminergic pathways (Halvern *et al.*, 1991). An alternative approach to controlling out of season breeding could involve appropriate use of antagonists of such a pathway or agonists of potentially inhibitory pathways, but first the background neuroendocrinology needs to be extrapolated from sheep to deer. In this regard, it is known that deer hinds have a major non oestrogen-dependent component in the control of seasonal breeding (Miekle and Fisher, 1996) which sets them apart from some sheep studies and there may be other species differences. So far we have explored a number of neurotransmitter pathways in red deer hinds and have indeed found this to be the case. Dopaminergic neurons are considered to be involved in mediating the negative feedback effects of oestradiol in sheep (Meyer and Goodman, 1985; Halvern *et al.*, 1991; Viguié *et al.*, 1996), thus implicating them in seasonal control of reproduction. Similarly, opioidergic pathways (i.e. involving endogenous opiates) may operate in the non oestrogen-dependent component of suppressed reproductive function in the ewe (Schillo *et al.*, 1985; Yang *et al.*, 1988; Schall *et al.*, 1991). However, in spite of rigorous study in red deer hinds, neither agonists or antagonists of these pathways had any effect on pulsing of luteinizing hormone secretion (Anderson and Barrell, 1998b). So far, our studies have shown that serotoninergic (i.e. involving serotonin, or 5-hydroxy tryptamine) pathways may have a stimulatory role in the control of reproduction in red deer hinds (Villa-Diaz and Barrell, 1999). The studies on red deer are preliminary and it is likely that more rigorous investigation will eventually reveal pathways with major influences on reproductive activity in this species. Hopefully, when this is the case such knowledge will lead swiftly to applications for controlling the season of calving in the deer farming industry.

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