The resurgence of clover disease in sheep: implications for industry and research directions

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Subterranean clover (*Trifolium subterraneum*) was probably introduced into Western Australia in the 1830s and has since become integral to pasture systems across southern Australia (Nicholls *et al*. 2013). In the 1940s, it was linked to severe infertility in sheep, 'clover disease' (Bennetts *et al*. 1946). The causative agent was found to be a group of non-steroidal phyto-oestrogens, one of which, formononetin, is demethylated in the rumen to form equol, a molecule that is structurally similar to the major ovarian sex steroid, oestradiol-17ß (E_2). In ewes, equol disturbs the brain control of reproduction, sexual behaviour, sperm transport and uterine function (Adams 1995).

By the 1990s, it was thought that four decades of successful research and development had banished 'clover disease' to history, largely because farmers avoided clover-dominant pastures and low-phytoestrogen cultivars had been developed and widely adopted. However, the disease is making a comeback, primarily because there has been a loss of corporate memory and skills in livestock managers, seed merchants, veterinarians, and government agencies. With the resurgence of high-oestrogen cultivars in pastures, more than 10 million sheep across Australia seem to be affected, at a potential cost of $500m pa (Walker *et al.* 2002).

We are ill-equipped to tackle this major problem because our current understanding of 'clover disease' is based on research done in the period 1950-1970, and most of the expertise and laboratories are long gone. On the other hand, the intervening decades have brought major technical advances that can be used to investigate the causative agents, the reproductive responses, and novel solutions. For example, we have identified the genes responsible for isoflavonoid production in the clover genome. Similarly, research on how the sheep rumen modifies dietary phyto-oestrogens was done long before the advent of molecular biology, bioinformatics, and *in vitro* rumen models, tools that have massively increased our understanding of the rumen microbiome and bacterial metabolic pathways. Finally, technological breakthroughs in cell biology offer a wide variety of new tools for investigating responses to phyto-oestrogens that reach the circulation of the sheep (Figure 1).

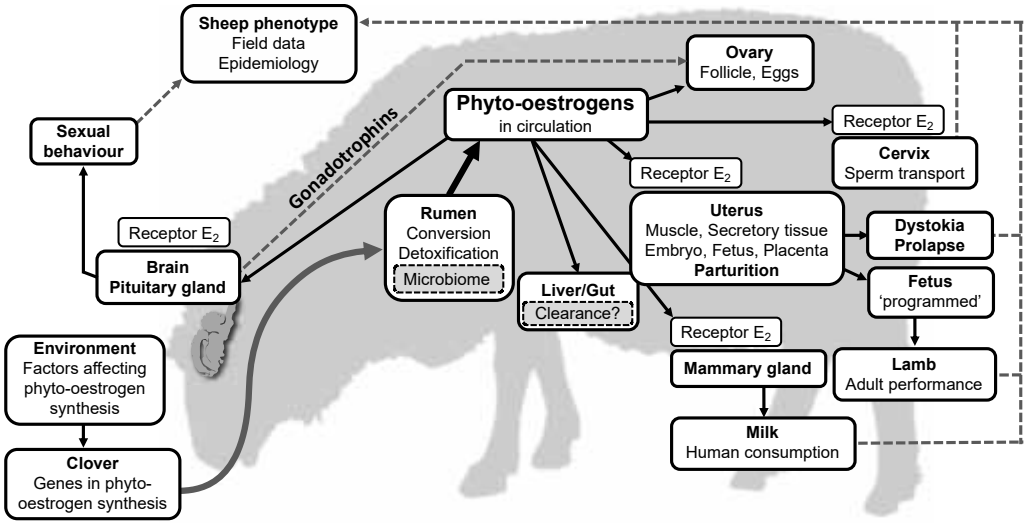

Figure 1. Potential sites of action for phytoestrogens in the reproductive processes in sheep.

We need a three-pronged attack on the problem: i) an extension program to inform industry about 'clover disease'; ii) training in field identification of high-oestrogen cultivars, and in selection of cultivars for pasture renovation; iii) research that takes advantage of modern technology so we can find new solutions.

References

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