THE MECHANISMS UNDERLYING GENETIC RESISTANCE TO *OSTERTAGIA CIRCUMCINCTA*

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Eight years ago Glasgow University Veterinary School set up a project to improve our understanding of the mechanisms underlying resistance to infection with *Ostertagia circumcincta* (also known as *Teladorsagia circumcincta*). The hope was that an increased understanding would lead to better and more sustainable methods of control.

This presentation will provide a brief overview of the immunological mechanisms underlying genetic resistance to *O. circumcincta* in lambs. Further details are provided in Stear *et al*. (1997a, 1997b). A commercial farm in Strathclyde was used to ensure that the results would be more applicable to sheep farmers. The sheep were purebred Scottish Blackface sheep. This breed was chosen because it is the most numerous breed in Europe and is widely used in both straightbreeding and crossbreeding schemes. Additionally, previous research at Glasgow had indicated that the breed was relatively resistant but that there was also substantial variation within the breed.

O. circumcincta is a remarkably successful parasite. Almost all grazing sheep in temperate areas are infected and many sheep carry thousands of worms. Although it is sometimes argued that livestock have high worm burdens because of commercial farming conditions, this does not explain why *O. circumcincta* is more successful than other parasites such as *Trichostrongylus axei*, *Trichostrongylus vitrinus* and *Cooperia spp*. The explanation for the relative success of *O. circumcincta* appears to lie in the ability of some individuals to survive over the winter, either inside the host, possibly as inhibited larvae or on pasture.

O. circumcincta can have a major impact on the growth of young lambs. Infected lambs grow much more slowly than their contemporaries and only a proportion of this loss can be recovered by anthelmintic treatment (Coop *et al*., 1982, 1985). Perhaps the best way of assessing the influence of infection on growth is to estimate the genetic correlation between growth rate and resistance to infection. The genetic correlation between faecal egg count and bodyweight is remarkably high at -0.8 (Bishop *et al*., 1996). Animals with breeding values for high egg counts have breeding values for low growth rate. Indeed, genetic correlations that are this strong suggest that the most important genes for growth rate in grazing animals are the genes for parasite resistance.

There are five key features of the interaction between lambs and *O. circumcincta* that are relevant to this presentation:

1. Resistance is acquired and not innate
2. Worm length is associated with fecundity
3. Worm length and hence fecundity declines as worm numbers increase
4. Lambs can control worm length but not worm number

5. IgA appears to be the major mechanism regulating worm length

Faecal samples were taken at monthly intervals every year for five years from five different cohorts of lambs. At each sample date every lamb was treated with an effective anthelmintic (albendazole sulphoxide) according to the manufacturers recommendations. Therefore each sample represents an independent infection. The number of nematode eggs in the faeces were counted according to a modified McMaster technique. The heritability of a single egg count in each month was estimated by standard methods (Bishop *et al*., 1996). The heritabilities were essentially zero at one and two months of age then rose rapidly to 0.33 at six months of age. In addition, the counts from 3 to 6 months of age had mutually significant positive phenotypic and genetic correlations. Further, the amount of variation increased as the lambs matured. The simplest conclusion is that little, if any, of the variation in faecal egg counts in one and two month old lambs was genetic in origin. Subsequent samples showed an increasingly strong genetic component. Therefore genetic resistance operates through control of an acquired response. The most likely acquired response is of course the immune response.

These heritabilities are sufficiently high to make selective breeding feasible. Taking multiple samples from animals at different ages and making replicate counts on each sample would increase the heritability even further. For example, four samples at 3 to 6 months of age and four counts on each sample would almost double the heritability. The favourable genetic correlation with growth rate means that it would be straightforward to decrease faecal egg counts and increase growth rate at the same time. In addition, the reduction in faecal egg count means that the amount of pasture contamination would also be reduced. The combination of increased resistance and decreased pasture contamination would lead to much greater reduction in faecal egg counts than that predicted by classical quantitative genetic theory (Bishop and Stear, 1997). For transmissible diseases, genetic theory probably underestimates the value of breeding for disease resistance.

Over 500 lambs were necropsied at 6-7 months of age, using published procedures. There was considerable variation among lambs in the mean length of adult female worms, with a two-fold range between the longest and the shortest (0.6 to 1.2 cm). Within the same lamb most worms are very similar in length. Male worms are shorter than female worms but there is a strong positive correlation between mean male and female worm length; lambs with long females have long males. Both deliberate and natural infections show a remarkably similar relationship between the mean length of mature female *O. circumcincta* and mean fecundity. In both cases fecundity = 1.1 (worm length) 0.4.

As worm numbers increase, there is a linear decline in worm length and fecundity. This could be due to crowding and competition for resources. Alternatively, increased numbers of worms could stimulate an increased immune response.

The heritability of worm number was not significantly different from zero (0.14 ± 0.10). There is no evidence in these data that any of the variation among lambs in worm number is genetic in origin and therefore no evidence for an effective acquired response that controls worm number. However, a weak response cannot be ruled out. Genetic variation in worm number is however insufficient to account for genetic variation in faecal egg count. In contrast, the heritability of worm length was extremely strong (0.62 ± 0.20). This high value suggests that genetic variation among hosts accounts for almost twice as much of the variation in mean worm length as all other factors combined, including genetic variation in the worms themselves. These heritabilities suggest that the major manifestation of resistance in lambs is the control of worm growth and fecundity, not the control of worm numbers.

Among the many immune responses investigated, the only response that is consistently associated with a reduction in worm length is the parasite-specific local IgA response. The strongest relationship was with the amount of IgA specific for fourth-stage larvae, as measured by indirect ELISA. Eight replicate IgA measurements gave an average correlation with mean adult female worm length of 0.38 (Stear *et al*., 1997a).

Some animals appear unable to control worm length despite having moderately strong IgA responses. One explanation is that they are unable to respond to the relevant parasite antigens. Western blotting with third-stage, fourth-stage or adult parasite preparations revealed extensive heterogeneity in antigen recognition (McCririe *et al*., 1997). No sheep was able to recognise all antigens and very few, if any, parasite molecules were recognised by antibody from all sheep. Statistical analyses have shown significant relationships between the recognition of four molecules and variation in adult *O. circumcincta* female worm length (McCririe *et al*., 1997).

The existence of a statistical relationship in a properly designed experiment could be direct (A is associated with B because A influences B) or indirect (A is associated with B because A influences C which influences B). Three factors are associated with variation in worm length: worm number, IgA response to fourth-stage larvae and specificity of the antibody response. When these three factors are considered together they account for the vast majority (> 90%) of the variation in worm length. This makes it unlikely that IgA is merely associated with the true effector mechanism. because no known immune response is sufficiently strongly associated with the IgA response. Therefore our working hypothesis is that worm length is controlled by the local IgA response. However, additional research is necessary, especially to confirm the importance of the four molecules in influencing worm length.

In summary, resistance to *O. circumcincta* is acquired and not innate. Worm length is a marker of worm fecundity. Worm length and hence worm fecundity are influenced by the number of worms within the host and by the strength and specificity of the IgA response.

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