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Review

Understanding parasitic infection in sheep to design more efficient animal selection strategies

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ABSTRACT

Modern livestock breeding practices provide new opportunities for producing animals that are adapted to their production environment and are free of disease. Using current knowledge of biology and by seeking 'the desired outcome' animal selection strategies can be designed that deliver more precisely defined results so maximising genetic gain and minimising risk. This review briefly describes the evolution of genetic selection in livestock and considers some of the positive and negative aspects of selection practices over time. The selection of sheep to withstand gastro-intestinal nematode parasitism is used as an example to explain how developments in selection strategy have improved genetic progress for complex traits.

Re-evaluation of the understanding of the outcomes of selection for parasite resistance is used here to examine whether a more sophisticated approach is desirable, and to propose a number of additional phenotype measurement strategies that could complement and improve the quality of information used for animal selection. Finally some ideas are presented for creating a situation where a designed, highly defined breeding objective might be used to increase precision and reduce risk. This may become possible via research to adapt or develop tools for more sophisticated phenotypic evaluation, to discover biological processes integral to desired breed changes, and to define desired animal types which match economic and societal expectations.

Introduction

In this review we briefly describe genetic selection in livestock and some of the positive and negative aspects of selection practices over time. Secondly, we use the selection of sheep to withstand gastro-intestinal nematode parasitism as an example to explain how developments in selection strategy have improved genetic progress for complex traits. Although a raft of species of nematode parasites infect sheep (23 genera are listed in Clunies Ross and Gordon (1936) and Whitlock (1960)), most published works focus on *Trichostrongylus colubriformis*, *T. vitrinus*, *Haemonchus contortus* and *Teladorsagia circumcincta*, so these are the main parasites we consider here.

Immune responses against parasitic organisms are complex, and this is a likely basis for parasite resistance behaving as a quantitative trait. Selection for a complex, immune system trait such as disease resistance adds complexity to a breeding objective, because the trait involves the interaction between both host and parasite genotypes, immune responses which follow multiple pathways to arrive at a variety of different immune phenotype outcomes, and can also involve complex interactions with commensal organisms (Honda and Littman, 2012). Longer term, complexity can be increased further because changes in the host can result in compensatory genetic changes in the parasite. Practically, sheep are a domestic livestock species and this influences the nature of objective measurement-based genetic programs, especially the need for high-throughput, inexpensive and simple phenotypic measurements of resistance.

The third aspect considered is a re-evaluation of our understanding of the outcomes of selection for parasite resistance. We ask if a more sophisticated approach is desired, and propose a number of additional phenotype measurement strategies which could be investigated further with the aim of complementing and improving the quality of information used for animal selection.

Breeding domestic livestock: A brief history

The domestication process began around 11,000 years ago when humans first began recruiting animals from the wild. Since then, man has sought to emphasise the desirable attributes of domestic animals through selective breeding. Information about

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the process of domestication and subsequent selection has been obtained from molecular analysis of existing livestock breeds (e.g., for sheep, see Meadows et al., 2007; Chessa et al., 2009), from archaeological analyses of finds (e.g. isotopic and lipid-based analyses; see Atahan et al., 2011; Outram et al., 2012) and literary sources (e.g. the records of commercial transactions of livestock in Mesopotamia during the 4th millennium BC; Carmona and Ezzamel, 2007).

Breeding and selection in a variety of mammalian species has resulted in phenotypes that differ markedly from the wild ancestor, but these alterations resulted because of both accidental and deliberate selection. Positive selection for phenotypes or traits considered beneficial is common. These have often included pigmentation traits, as animal breeders have long shown a preference for their animals to display characteristic patterns (e.g. Black Angus cattle or red Duroc pigs). The consequence is that the DNA mutations that underpin particular coat colour patterns will be selected within the population and over time they may even reach fixation. Other examples of positive selection involve production traits such as muscularity. The myostatin gene (GDF8) gene carries mutations in a number of species that confer a hypermuscularity trait. It has undergone positive selection in cattle (e.g. the double muscled Belgian Blue) and sheep (e.g. the Texel breed).

Some mutations can also be found at high frequency because of random processes, sometimes exacerbated by geographical or cultural isolation. A mutation in the MDR1 gene present in some dog breeds was presumably neutral when it occurred some time before 1900 (Neff et al., 2004; Geyer et al., 2005). After the use of ivermectin became widespread, it was discovered that dogs carrying the MDR1 deletion displayed a range of neurological symptoms in response to drug treatment; the allele was no longer neutral, but deleterious. Some alleles however can be deleterious from the moment they occur, and these are subject to negative selection from the outset. Ancient selection practices are likely to have resulted in the loss of many deleterious mutations over time, as occurs in natural populations.

Some deleterious alleles can linger in populations due to founder effects or genetic drift, especially in small populations which have fewer genetic links to outside populations. For example, ovine hereditary chondrodysplasia (Spider Lamb Syndrome) caused by an allele of the FGFR3 gene of sheep (Beever et al., 2006) was prevalent in some breeds until direct selection against the allele became possible. There are a complex set of other scenarios which drive natural selection, and for those wishing to read more, an example of a recent text dealing with many of these population genetic principles is Hartl and Clark (2007).

In the late 18th and early 19th centuries, breeding became more directed and the recombination of breeds into new types became important globally (Matz, 2010). Subsequently, the development of modern genetic theory during the early 20th century led to objective measurement and rigorous phenotypic selection both to increase genetic progress towards desirable outcomes and to develop strategies to remove undesirable genotypes. As this methodology became more sophisticated (see, for example, Henderson, 1984), selective breeding for traits which are much harder to measure became possible (e.g. pathogen resistance) and selection for traits which are controlled by many genes (e.g. polygenic traits) became more efficient. Breeding and selection strategies continue to evolve to this day, and the possibility of selection based directly on genome sequence information is now an actuality for some farmyard species (Goddard et al., 2010).

Even with the implementation of more sophisticated methodology, selection programs can sometimes result in deleterious outcomes. For example, many veterinarians will be familiar with some genetic conditions which have been linked to dog breed standards (e.g. Asher et al., 2009). During the late 19th and early 20th centuries heavily wrinkled sheep of the Vermont Merino strain were introduced to Australia and crossed with existing Merino flocks. This resulted in a highly wrinkled skin morphology that inadvertently left the breed highly susceptible to cutaneous myiasis (Seddon, 1931). The widespread adoption of crossing with the Vermont resulted in biological consequences which still plague the industry and the resulting economic cost has forced alterations to genetic selection and animal management practices (Scholtz et al., 2010; Sneddon and Rollin, 2010).

In other examples, deleterious outcomes have been avoided through an understanding of the trait under selection and the impact of this selection on another trait of importance. One example of this is the undesirable correlation of fleece weight and fibre diameter in sheep, where a widespread knowledge of this issue has helped breeders combine the two traits in a selection index and to achieve genetic progress increasing fleece weight and reducing fibre diameter. Unfortunately, few studies have generated genetic correlations between disease susceptibility traits in mammals, but the importance of doing so is exemplified by recent data showing an unfavourable correlation between predisposition for *Mycobacterium bovis* infection and somatic cell count (a measure of mastitis) in Irish dairy cattle (Bermingham et al., 2010). The discovery of such correlations can be fertile ground for the development of hypotheses, but subsequent work can reveal that the interactions are more complex than expected. For example, the relationship between resistance to gastro-intestinal nematodes in sheep and resistance to sheep lice (*Bovicola ovis*) has been investigated multiple times with differing results (e.g. compare Pfeffer et al. (2007) with James et al. (2002)).

The selective breeding of animals from ancient times through to the present day has resulted in genetic changes through both deliberate and accidental processes. Modern molecular genetic techniques have enabled us to analyse the history of allelic variants of genes and their role in populations of animals, and the influence of molecular genetics in animal selection has begun to have a much wider impact in recent years. Changing environments or production systems combined with incomplete knowledge of the set of important traits can all contribute to non-desirable selection outcomes. Modern selection methodology seeks to use more information in an objective way to minimise risk, but for some traits such as disease resistance, this process can be a challenge.

Selection of animals to enhance disease resistance

Resistance to infection is the ability of a host to withstand the effects of an infective agent by blocking invasion and/or by eliminating organisms that have invaded host tissues. In contrast there are the alternative attributes of resilience, where the infective agent can invade host tissues and establish itself (but the host is able to avoid the resulting pathological effects), and avoidance, where the host is able to avoid exposure to the infective agent by modifying its behaviour. In each of these examples successful selection of superior animals is dependent on accurate measurement of infection load, immune response, and production status or disease pathology.

To obtain such measurements can be difficult, expensive and/or time consuming. For example, pathogen incidence may be sporadic preventing selection opportunities in some generations. The need to minimise harm and optimise welfare and/or production can also place a constraint upon measuring disease resistance, limiting for example the ability to conduct deliberate infections as part of the process. Some diseases also progress very quickly, so that it is difficult to measure reliably every individual during the same phase of infection (for example foot-and-mouth disease). Most measures of resistance are not obtainable in the unexposed, naïve animal.