DISEASE SUSCEPTIBILITY, STRESS AND WELFARE: A LINK

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Resistance and Genetics

Resistance to infectious disease is strongly influenced by both the genetic make-up of individuals (*genotype*)[1] and the environmental factors (*stressors*)[2] to which they are exposed, throughout their lives Genetic resistance varies between different species and also within individual members of a particular species of animal The genetic markers which influence susceptibility to disease include genes that code for innate (*non-specific*) resistance (Bcg/Nramp)[1] and the major histocompatibility glycoproteins (MHC)[3] These mediate macrophage killing of infectious organisms and immunocompetence in the development of specific acquired immunity, respectively Genetic differences also exist in the adrenal responsiveness of animals to stressful stimuli[4]

Stress

It would be considered unusual for any group of animals not to be confronted with stressful situations, whether they be found in the wild, on the family farm or in a commercial operation Stress can be viewed as the result of an imposed factor, but it can also be considered as the consequence of a loss of control This may be reduced further, to describe stress as resulting from a loss of natural preference, free movement, company, self determined speed, vital space or free interaction Examples of stressors commonly found in the farm setting are detailed in table I

TABLE I
Management stressors which influence farmed deer.

MANAGEMENT	*transportation* *drafting/restraint* *drugs/vaccines* *velvetting* *surgery/tagging* *overcrowding* *poor nutrition*	ENVIRONMENTAL	*extremes in climate* *infectious agents* *physical injury* *novel sights/sounds*
		PSYCHOSOCIAL	*separation at weaning* *separation from peers* *hierarchical/fighting*

Both physical and psychological stressors elicit responses developed to reduce the impact of stress and restore balance or homeostasis [5] These include physiological responses, immunological mechanisms and behavioural adaptations which allow animals to react to these stressful events A variety of endocrine changes including activation of the sympathetic-adrenomedullary axis (SPA) and/or the hypothalamic-pituitary-adrenal (HPA) axis are manifest during the individual's response to stress [6] Deer exhibit a vigorous SPA response to acute stress, the autonomic nervous system and the adrenal medulla forming the basis for Cannon's *fight/flight* response [7] Hyperactivity of the HPA axis is accompanied by increased secretion of corticotropic releasing hormone, which stimulates the release of ACTH by the pituitary gland ACTH binds receptors on the adrenal gland, in completing the HPA axis, causes an increase in the production of glucocorticoid hormones (GC) [8]

Acute v Chronic Stress

In general the *'stress response'* functions beneficially at an acute level with few adverse consequences (and even some immune potentiation), although if it is activated chronically, without appropriate adaptation, suppression of vital immune function may result[8] Glucocorticoid hormones secreted in response to chronic stress or prolonged activation of SPA are known to increase the susceptibility of animals to infectious disease, by exerting profoundly suppressive effects on the immune system[9], altering genetic susceptibility levels by a number of mechanisms

Experimental Animal Studies

Extensive studies have been carried out in mice to evaluate the effects of stress on the response to mycobacteria, by strains which are different genetically in their resistance profiles Activation of the HPA axis via stress, can increase the *in vivo* growth of mycobacteria in genetically susceptible *(Bcg_s)* genotypes, but does not alter the growth in resistant *(Bcg_r)* animals [2] This is not a reflection of any unresponsiveness by these different strains to stress *per se,* as the levels of GC produced are equivalent [10] Furthermore, the capacity of macrophages from both genotypes, to function as assessed by their production of anti-mycobacterial factors, such as tumour necrosis factor (TNF-α) and reactive nitrogen intermediates (NO_2^-) is suppressed to the same extent in both strains, in response to stress [2]

The levels of MHC-II glycoprotein expression are suppressed differentially in Bcg_r and Bcg_s strains following HPA activation [11] (ie MHC-II expression is suppressed in Bcg_s but remains unaffected in Bcg_r) although the induction, by an activated immune response, of MHC-II expression is equally affected in both strains Thus the temporal aspects of stress exposure relative to infection are critical, in that once the acquired immune response is established the effects of stress are attenuated

High and Low Stress Responders

Variations also exist in the magnitude at which individuals respond to stress High and low responders have been identified on the basis of the magnitude of corticosteroids(GC) produced

in response to identical stimuli *'Low stress responders'* tend to retain a more vigorous cell mediated immune response (CMI) compared to their humoral immune response (HI) and tend to be more resistant to intracellular pathogens, whereas *'high stress responders'* tend to have a higher level of HI activation at the expense of CMI [4]

In an outbred population it is expected that in situations where extrinsic levels of stress are high, those individuals with genetically predetermined high GC stress responses, will be most at risk from infectious diseases requiring a CMI response for their eradication [4] This means that chronic stress (eg overcrowding, poor nutrition, extremes in climate or hierarchical interactions) could cause suppression of innate resistance or acquired cellular immunity to produce a compromised animal with increased susceptibility to disease caused by intracellular bacteria (tuberculosis), viruses (MCF) and parasites (both gut and lung), while leaving humoral immunity relatively intact

Optimal Management

The most extreme impact of environmental stress was seen early in the domestication of deer where stress associated with capture and adaptation to intensive farming produced high levels (25%) of fatal infectious disease and pathophysiological conditions such as post-capture myopathy While there was an initial perception that cervidae were more genotypically susceptible to diseases such as bovine tuberculosis (Tb), this has not been borne out by subsequent observations of Tb in deer The florid presentation of Tb infection in deer herds throughout the 1980's may have been due more to limitations in management practices rather than unique genotypic susceptibility of deer, to infectious disease The altered patterns of infection found in farmed deer over the past twenty years, may represent the removal of genetically susceptible animals from the gene pool by selective pressure, but is more likely a reflection of the superior handling and management systems currently in place, which have improved the overall health, well-being and therefore, disease resistance of animals within our national deer herd We have confirmed many of the preceeding statements experimentally, over the past few years Table II summarises some of our results

TABLE II

Experimental data linking stress with immune competence and disease susceptibility.

STRESSOR	PARAMETER	EFFECT	REF
Transport	yersiniosis prevalance	**increase**	12
	yersiniosis severity	**increase**	12
	antibody production[1]	**no change**	13
Weaning[2]	antibody production[1]	**no change**	14
	lymphocyte function[3]	**no change**	14
Capture	lymphocyte function[3]		
	¥ high ACTH responders[4]	**decrease**	15
	¥ low ACTH responders	**increase**	15
	¥ needle shy animals	**increase**	15
GC administration[5]	yersinia seroconversion	**increase**	
	Johnes vaccine response	**decrease**	16
	Tb- severity (experimental challenge)	**increase**	16
	BCG vaccination (protective efficacy)	**decrease**	

1- Antibody (class-G) to primary vaccination with the protein antigen, keyhole limpet haemocyanin (KLH).
2- Normal weaning according to sound farming practice
3- Specific lymphocyte function assessed by proliferation stimulated by KLH, following vaccination, see 1.
4- GC response following stimulation with ACTH.
5- Corticosteroid administration as a model to simulate stress

Conclusion

Deer farming has presented a unique challenge for intensive adaptation of a large species of wild animal to farming practice during this century Early failure to provide appropriate adaptation regimes for farmed deer provided evidence of the apparent unique susceptibility of cervidae to infection, whereas retrospection allows us to revisit these concepts It has become evident that well adapted farmed deer are no less resistant to intercurrent infection than other farmed ruminants Susceptibility to infection has been more due to phenotypic modification than

genotypic defects The success of cervids in colonising every habitat available within our ecosystem which is utilised by ruminants, provides evidence for the genotypic robustness of this genus

The diversity of their target immune molecular glycoproteins (MHC)[17] attests to their anthropologic potential to cope with diverse challenges from a variety of virulent infectious diseases New Zealand deer farmers have responded to the challenge of providing an ambient environment to maximise the phenotypic potential of farmed cervids The information we have gained in deer farming provides salutory lessons for wildlife management and shows that the industry has evolved to recognise that, the production of animals and their well-being is inexorably linked by immune physiology

Ultimately how well deer farmers can maximise the health and well-being of their animals will reflect their productive potential, smart farmers will reach the conclusion that pragmatism, if not altruism, will maximise the productivity of their livestock

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