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On the adaptive significance of stress-induced immunosuppression

Lars Råberg*, Mats Grahn, Dennis Hasselquist and Erik Svensson†

Department of Animal Ecology, Lund University, Ecology Building, S-223 62 Lund, Sweden

We approach the field of stress immunology from an ecological point of view and ask: why should a heavy physical workload, for example as a result of a high reproductive effort, compromise immune function? We argue that immunosuppression by neuroendocrine mechanisms, such as stress hormones, during heavy physical workload is adaptive, and consider two different ultimate explanations of such immunosuppression. First, several authors have suggested that the immune system is suppressed to reallocate resources to other metabolic demands. In our view, this hypothesis assumes that considerable amounts of energy or nutrients can be saved by suppressing the immune system; however, this assumption requires further investigation. Second, we suggest an alternative explanation based on the idea that the immune system is tightly regulated by neuroendocrine mechanisms to avoid hyperactivation and ensuing autoimmune responses. We hypothesize that the risk of autoimmune responses increases during heavy physical workload and that the immune system is suppressed to counteract this.

Keywords: cost of reproduction; immunocompetence; sexual selection; strenuous exercise

1. INTRODUCTION

There is accumulating evidence from studies of humans and laboratory animals that stress, such as strenuous exercise and cold exposure, can suppress the immune system (Sapolsky 1992; Hoffman-Goetz & Pedersen 1994; Nieman & Nehlsen-Cannarella 1994). Investigations of this area of medicine and physiology have concentrated mainly on how stress causes immunosuppression (a mechanistic perspective), whereas the question of why these processes occur at all (an evolutionary perspective) is more rarely addressed.

It has recently been hypothesized that the immune system could be an important mechanism in the evolution of behaviour, especially in the contexts of life-history strategies and sexual selection (reviewed in Zuk (1992) and Sheldon & Verhulst (1996)). Behaviours such as sexual display and nestling feeding in birds are similar to strenuous exercise in that they impose a high metabolic rate (e.g. Vehrencamp *et al*. 1989; Masman *et al*. 1989), and can therefore be considered ecologically relevant stress. Hence, it is plausible that there is a physiological trade-off between immune defence and costly behaviours (Følstad & Karter 1992; Wedekind 1992; Gustafsson *et al*. 1994; Wedekind & Følstad 1994; Deerenberg *et al*. 1997; Demas *et al*. 1997). The evolutionary significance of such a trade-off can be illustrated with a recent hypothesis from life-history theory.

The concept of a 'cost of reproduction' (Williams 1966) is central to life-history theory and is defined as a decrease in expected future reproductive output as a consequence of current reproductive effort. The detailed mechanisms mediating these effects remain largely obscure, but long-term reproductive costs (e.g. reduced future fecundity (Gustafsson & Sutherland 1988) or survival (Daan *et al*. 1996)) must undoubtedly be mediated by physiological mechanisms. It has been hypothesized that a high level of reproductive effort could compromise an individual's immune defence, thereby increasing its susceptibility to infectious disease, which in turn could reduce survival and/or future reproductive performance (Gustafsson *et al*. 1994; Deerenberg *et al*. 1997), and there is some empirical support for this hypothesis (e.g. Richner *et al*. 1995; Deerenberg *et al*. 1997). The immune system could thus serve as a physiological mechanism mediating reproductive costs. But why should a heavy physical workload, for example as a result of a high reproductive effort, compromise immune function?

2. ADAPTIVE OR NON-ADAPTIVE IMMUNOSUPPRESSION

The simplest explanation of immunosuppression during heavy physical workload is that there is an increased wear and tear of body functions. This could be caused by the increased formation of detrimental waste products, for example oxygen free radicals, which have a non-specific, damaging effect on tissue, including the immune system (e.g. Jenkins 1993; Bendich 1996). This is an obvious example of non-adaptive immunosuppression; free radicals did not evolve to suppress the immune system but are an undesired consequence of a high metabolic rate. Although this non-adaptive mechanism is potentially important, it is at least not the only explanation of stress-induced immunosuppression. The neural and

*Author for correspondence (lars.raberg@zooekol.lu.se).
†Present address: UCSC, Department of Biology, Organismal and Population Biology, Santa Cruz, CA 95064, USA.

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hormonal regulation of the immune system, in particular by glucocorticoids (stress hormones) (Besedovsky & del Rey 1995), provides another explanation of stress-induced immunosuppression. We will use glucocorticoids as an example and argue that such mechanisms can only be interpreted as adaptations.

Stress, such as strenuous exercise, cold exposure, infection or trauma activates the hypothalamic–pituitary–adrenal axis, and one of the major consequences of this is increased plasma levels of glucocorticoid steroids (Sapolsky 1992; Galbo 1995; Kapcala *et al*. 1995). Glucocorticoids affect various body functions, for example the metabolic and cardiovascular systems, to maintain homeostasis during stress, an effect that is undoubtedly adaptive (Sapolsky 1992; Munck & Náray-Fejes-Tóth 1995*b*). Glucocorticoids are also largely immunosuppressive (Sapolsky 1992; Wick *et al*. 1993; Munck & Náray-Fejes-Tóth 1995*b*; Marsh 1996; McEwen *et al*. 1997), a seemingly maladaptive effect. However, the effects of glucocorticoids on the immune system, as well as on other functions, are mediated via specific intracellular receptors regulating transcription of particular genes (Munck & Náray-Fejes-Tóth 1995*b*). The complex architecture of this mechanism and the 'observed conformity to *a priori* design specifications' (Williams 1992, p. 40) strongly suggests that it is designed by natural selection, rather than an incidental biochemical process. But what is the adaptive significance of such neuroendocrine suppression of the immune system during stress?

3. RESOURCE LIMITATION

'Ecological immunology' (Sheldon & Verhulst 1996) is currently focused on a resource-based trade-off between the immune system and costly behaviours as the ultimate explanation of stress-induced immunosuppression (Wedekind 1992; Gustafsson *et al*. 1994; Wedekind & Følstad 1994; Deerenberg *et al*. 1997; Demas *et al*. 1997). Following the 'principle of allocation' (Levins 1968), it is assumed that different functions compete for limited resources (the internal supply of energy or nutrients), and that investment in costly behaviours reduces the amount of resources available to immune defence. The allocation of resources among functions must be accomplished through specific regulation of the activity (and, hence, energy demand) of the respective functions, and this can only be achieved through neural or hormonal communication with the organs involved. The neuroendocrine–immune interactions mentioned above provide the mechanisms necessary for regulation of the immune system. Hence, glucocorticoids and resource limitation are not alternative explanations to immunosuppression by costly behaviours, but represent different levels of explanation, that is proximate and ultimate causes, respectively (see also Wedekind 1992; Wedekind & Følstad 1994).

This resource-limitation hypothesis requires that there is an energetic or nutritional cost associated with the immune system. We propose that there are two ways in which immune defence can be costly in terms of resources. First, it may be costly to maintain a well-functioning immune system; that is, if the running cost of the immune system (e.g. maintenance of lymphoid tissue, turnover of leucocytes) constitutes a substantial part of the daily turnover of energy or nutrients. Second, it may be costly to mount an immune response in the case of infection. Hence, the function of immunosuppression by neuroendocrine mechanisms during stress could be to reallocate resources from the maintenance cost, or to avoid the cost of mounting an immune response, or both.

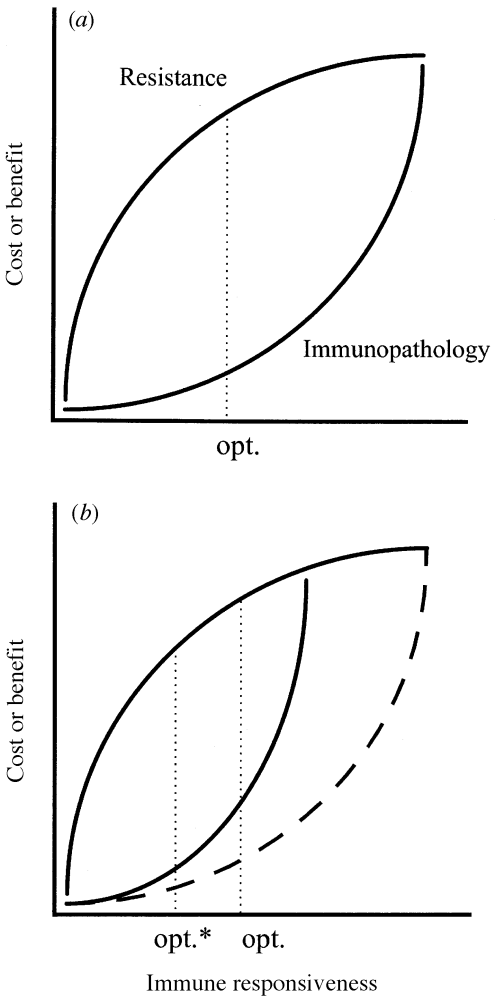

Figure 1. (*a*) Hypothetical cost (immunopathology) and benefit (resistance to parasites) curves as a function of immune responsiveness, and the optimal solution to this trade-off (opt.). (*b*) The cost function (immunopathology) varies depending on the state of the organism. During stress there is a change in the self-antigen repertoire that stimulates the immune system and could cause immunopathological responses. Consequently, the cost curve will be steeper and optimal immune responsiveness (opt.*) will be reduced.

4. AVOIDANCE OF IMMUNOPATHOLOGY

We here suggest an alternative function for neuroendocrine suppression of the immune system during heavy physical workload. The immune system is a potent weapon against parasites (from viruses to fleas), but also potentially harmful to the host. A high immune responsiveness increases resistance to parasites, but also increases the risk of immunopathology (such as an autoimmune response). Thus, there is a trade-off between the benefit of resistance to parasites and the cost of immunopathology (Behnke *et al*. 1992; Cannon 1993; Kapcala *et al*. 1995), and immune responsiveness should be carefully

optimized with respect to this trade-off. We use a simple graphical cost–benefit model (see also Behnke *et al*. 1992) to illustrate this (figure 1).

An infectious challenge, or tissue damage caused by trauma, not only stimulates the immune system to produce an immune or inflammatory response, but also activates neuroendocrine mechanisms, in particular glucocorticoid secretion, which eventually suppress the immune system (Besedovsky *et al*. 1985). The prevailing view among physiologists is that the function of immunosuppression by glucocorticoids during stress in the form of infection or trauma is to avoid hyperstimulation of defence mechanisms and ensuing immunopathology (Craddock 1978; Munck *et al*. 1984; Besedovsky *et al*. 1985; Munck & Náray-Fejes-Tóth; 1995*a*,*b*; Besedovsky & del Rey 1996). But why does stress in the form of strenuous exercise activate similar neuroendocrine mechanisms and consequently suppress the immune system?

Tolerance to self is to a large extent established during early ontogeny, and later changes in the self-antigen repertoire available to the immune system can induce autoimmune responses. Such tolerance-breaking changes could occur either as an increase in concentration of a self-antigen to which tolerance is maintained at lower concentrations, or appearance of a previously sequestered self-antigen to which tolerance has never been established (Rose & Mackay 1992; Theofilopoulos 1995). Hence, temporal quantitative or qualitative changes in the self-antigen repertoire available to the immune system will make it more dangerous to use the immune system; that is, the cost function (risk of immunopathology) will be steeper (figure 1*b*). Stress in the form of a heavy physical workload could cause such changes in at least two ways.

1. A heavy physical workload leads to muscle damage (Fielding *et al*. 1993; Woods *et al*. 1993; Camus *et al*. 1994), which could change the self-antigen repertoire and stimulate the immune system in a similar way as tissue damage caused by trauma (Craddock 1978; Cannon & Kluger 1983; Weight *et al*. 1991). It might therefore be necessary to suppress the immune system to limit the response and avoid immunopathology, as also suggested by Bagby *et al*. (1994).
2. Heat-shock proteins (or stress proteins) are found in all organisms and are very conserved phylogenetically (Locke & Noble 1995). They confer protection to the cell against environmental stress, and cells express higher levels of heat-shock proteins in response to a wide array of stress factors, including exercise (Locke & Noble 1995; Ornatsky *et al*. 1995). Heat-shock proteins of the pathogen are often targets of the host's immune response (Lamb *et al*. 1989). Because heat-shock proteins of the host and the pathogen are similar, there is a risk of cross reactivity (Haregewoin *et al*. 1991). In accordance, heat-shock proteins are often ascribed a role in autoimmunity (Winfield & Jarjour 1991). During stress, when host heat-shock proteins are expressed at a higher level (Locke & Noble 1995), the risk of autoreactivity should increase. Thus, heat-shock proteins provide an additional mechanism that could increase the risk of immunopathology during stress.

Based on this, we suggest the following model. There is a trade-off between resistance to parasites and immunopathology, and the optimal solution to this trade-off varies depending on the state of the individual organism. Heavy physical workload leads to a change in the self-antigen repertoire, which increases the risk of immunopathology (see above). To counteract this, and avoid inappropriate immune responses, the immune system is suppressed, at the expense of resistance to parasites (figure 1*b*).

5. DISCUSSION

Resource limitation and avoidance of immunopathology are fundamentally different, although not mutually exclusive, ultimate explanations of immunosuppression by neuroendocrine mechanisms during stress in the form of heavy physical workload. The inherent simplicity of a resource-based trade-off between immune defence and various costly activities is appealing, and this idea is often the foundation, more or less explicit, in ecological studies on host–parasite interactions. This hypothesis requires that immune defence is costly in terms of energy and/or nutrients. Fever is one important component of immune defence that carries substantial energetic costs (Baracos *et al*. 1987). Direct estimates of energetic costs of immune responses are rare, but Demas *et al*. (1997) found that mice immunized with keyhole-limpet haemocyanin had higher metabolic rates than control mice. On the other hand, in an experimental test of the hypothesis of a resource-based trade-off between immune defence and costly behaviours, Svensson *et al*. (1997) found that cold-stressed blue tits had lower immune responses to a vaccine than control birds, but that this could not readily be explained with resource limitation, because the energetic cost of this immune response was very low. Two reports give indirect evidence that immune responses are costly in terms of energy and/or nutrients: chickens immunized with lipopolysaccharide or sheep red blood cells had reduced weight-gain (Klasing *et al*. 1987), and, similarly, adult zebra finches immunized with sheep red blood cells had lower weight-gain towards the end of nestling feeding than control birds (Deerenberg *et al*. 1997). However, in our view, a resource-based trade-off between immune defence and, for example, reproductive effort, requires not only that immune defence shows demonstrable energetic costs, but also that the fitness costs (in terms of reduced residual reproductive value) of reallocation of a given amount of resources from immune defence to reproduction are comparable to the fitness benefits (in terms of increased current reproductive success) and vice versa. This is currently very difficult to assess, because nothing is known about the costs of mounting immune responses to a relevant pathogen, nor about the maintenance costs of the immune system, and the potential for a resource-based trade-off must be therefore be considered an open question, well worth further study. Meanwhile, we agree with the view of Sapolsky (1992), that the mechanisms involved in suppressing the immune system during stress, for example apoptosis (programmed cell death) of functional leucocytes, seem

poorly designed to save energy or nutrients, such that other explanations should also be considered.

The prevailing view among physiologists is that the function of neuroendocrine suppression of the immune system during infection and trauma is to eventually restrain the response and restore immune system activity to normal levels, thereby avoiding hyperactivation of the immune system and ensuing autoimmune responses (Craddock 1978; Munck *et al*. 1984; Besedovsky *et al*. 1985; Munck & Náray-Fejes-Tóth 1995*a*,*b*; Besedovsky & del Rey 1996). We have extended this idea to provide a potential explanation as to why it could be adaptive to suppress the immune system and sacrifice some of the ability to fight invading parasites during heavy physical workload; namely because the organism anticipates a stimulation by innocuous self-antigens to which a response would do more harm than good.

There is firm evidence of a genetic component (i.e. major histocompatibility complex (MHC) genotype) to the risk of developing autoimmune disease, and studies of heat-shock proteins provide a particularly good example of this (Lamb *et al*. 1989; Jones *et al*. 1993). Immune responses to microbial heat-shock proteins could lead to autoimmune responses because of cross-reactivity with host heat-shock proteins. The risk of cross-reactivity may depend on an individual's MHC class II genotype (Lamb *et al*. 1989; Jones *et al*. 1990). The important ecological implication of this is that if heavy physical workload increases the risk of autoimmune responses, individuals with low-risk MHC genotypes could still maintain a higher immune responsiveness at a given workload than high-risk individuals (see also Westneat & Birkhead 1998).

Adaptive immunosuppression to avoid inappropriate immune responses, rather than to save resources, has been suggested in at least three other contexts: (i) during metamorphosis in tadpoles to avoid immune responses to arising adult-specific self-antigens (Flajnik *et al*. 1987); (ii) testosterone-mediated immunosuppression to avoid autoimmune responses to sperm (Følstad & Skarstein 1997; Hillgarth *et al*. 1997); and (iii) suppression (of at least some components) of maternal immune system during pregnancy to avoid immune responses to the foetoplacental unit (Wegmann *et al*. 1993). Hence, quantitative and qualitative changes in the self-antigen repertoire are possibly common challenges, and the multitude of pathways between the neuroendocrine and immune systems may have evolved to optimize the trade-off between parasite resistance and immunopathology under the prevailing conditions.

A more detailed understanding of the energetic or immunopathologic costs associated with different components (e.g. humoral or cellular) of the immune system, and which components are, or are not, purposely suppressed in different situations, could give insight into the ultimate causes of immunosuppression in response to stress. If some components of the immune system are particularly costly (in terms of resources), and these components are suppressed by neuroendocrine mechanisms during stress, this would favour the resource-limitation hypothesis. Alternatively, if some components are particularly dangerous (in terms of immunopathology), and these components are suppressed, this would favour the immunopathology-avoidance hypothesis. Although far from fully understood, there are a number of studies on differential neuroendocrine regulation of the immune system (McEwen *et al*. 1997), as well as on the association between various components of immune defence with autoimmune disease (Theofilopoulos 1995). Furthermore, direct measures of the metabolic costs of mounting an immune response are beginning to emerge (Demas *et al*. 1997; Svensson *et al*. 1998). Estimates of maintenance costs of the immune system are lacking, but a tractable way to measure such costs could be to compare basal metabolic rates of normal mice with that of mouse strains lacking various components of the immune system.

Another way to disentangle these hypotheses would be to perform a phenotypic (for example by using glucocorticoid antagonists) or genotypic (for example by using Fisher and Lewis rats; these strains are very similar but the latter has a defect neuroendocrine response to stress) manipulation that renders the immune system resistant to neuroendocrine regulation and study if heavy physical workload results in depletion of resources or immunopathological responses (or both).

Elucidating the relative importance of the causes for stress-induced immunosuppression outlined here would certainly increase our understanding of the basis of trade-offs, such as between current and future reproduction.

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REFERENCES

Bagby, G. J., Sawaya, D. E., Crouch, L. D. & Shepherd, R. E. 1994 Prior exercise suppresses the tumour necrosis factor response to bacterial lipopolysaccharide. *J. Appl. Physiol*. **77**, 1542–1547.

Baracos, V. E., Whitmore, W. T. & Gale, R. 1987 The metabolic cost of fever. *Can. J. Physiol. Pharmacol*. **65**, 1248–1254.

Behnke, J. M., Barnard, C. J. & Wakelin, D. 1992 Understanding chronic nematode infections: evolutionary considerations, current hypotheses and the way forward. *Int. J. Parasitol*. **22**, 861–907.

Bendich, A. 1996 Antioxidant vitamins and human immune responses. *Vitamins Horm*. **52**, 35–62.

Besedovsky, H. O. & del Rey, A. E. 1996 Immune–neuro-endocrine interactions: facts and hypotheses. *Endocr. Rev.* **17**, 64–97.

Besedovsky, H. O., del Rey, A. E. & Sorkin, E. 1985 Immune–neuroendocrine interactions. *J. Immunol*. **135**, 750S–754S.

Camus, G., Deby-Depont, G., Duchateau, J., Deby, C., Pincemail, J. & Lamy, M. 1994 Are similar inflammatory factors involved in strenuous exercise and sepsis? *Intensive Care Med*. **20**, 602–610.

Cannon, J. G. 1993 Exercise and resistance to infection. *J. Appl. Physiol*. **74**, 973–981.

Cannon, J. G. & Kluger, M. J. 1983 Endogenous pyrogen activity in human plasma after exercise. *Science* **220**, 617–619.

Craddock, C. G. 1978 Corticosteroid-induced lymphopenia, immunosuppression, and body defense. *Ann. Int. Med*. **88**, 564–566.

Daan, S., Deerenberg, C. & Dijkstra, C. 1996 Increased daily work precipitates natural death in the kestrel. *J. Anim. Ecol*. **65**, 539–544.

Deerenberg, C., Apanius, V., Daan, S. & Bos, N. 1997 Reproductive effort decreases antibody responsiveness. *Proc. R. Soc. Lond.* B **264**, 1021–1029.

Demas, G. E., Chefer, V., Tala, M. I. & Nelson, R. J. 1997 Metabolic costs of mounting an antigen-stimulated immune response in adult and aged C57BL/6J mice. *Am. J. Physiol.* **273**, R1631–R1637.

Fielding, R. A., Manfredi, T. J., Ding, W., Fiatarone, M. A., Evans, W. J. & Cannon, J. G. 1993 Acute phase response in exercise. III. Neutrophil and IL-1β accumulation in skeletal muscle. *Am. J. Physiol.* **265**, R166–172.

Flajnik, M. F., Hsu, E., Kaufman, J. F. & du Pasquier, L. 1987 Changes in the immune system during metamorphosis of *Xenopus*. *Immunol. Today* **8**, 58–64.

Følstad, I. & Karter, A. J. 1992 Parasites, bright males, and the immunocompetence handicap. *Am. Nat.* **139**, 603–622.

Følstad, I. & Skarstein, F. 1997 Is male germ line control creating avenues for female choice? *Behav. Ecol.* **8**, 109–112.

Galbo, H. 1995 Integrated endocrine responses and exercise. In *Endocrinology* (ed. L. J. DeGroot and others), pp. 2692–2701. Philadelphia, PA: W. B. Saunders.

Gustafsson, L. & Sutherland, W. J. 1988 The costs of reproduction in the collared flycatcher *Ficedula albicollis*. *Nature* **335**, 813–815.

Gustafsson, L., Nordling, D., Andersson, M. S., Sheldon, B. C. & Qvarnström, A. 1994 Infectious diseases, reproductive effort and the cost of reproduction in birds. *Phil. Trans. R. Soc. Lond.* B **346**, 323–331.

Haregewoin, A., Singh, B., Gupta, R. S. & Finberg, R. W. 1990 A mycobacterial heat-shock protein-responsive γδ T cell clone also responds to the homologous human heat-shock protein: a possible link between infection and immunity. *J. Infect. Dis.* **163**, 156–160.

Hillgarth, N., Ramenofsky, M. & Wingfield, J. 1997 Testosterone and sexual selection. *Behav. Ecol.* **8**, 108–109.

Hoffmann-Goetz, L. & Pedersen, B. K. 1994 Exercise and the immune system: a model of the stress response? *Immunol. Today* **15**, 382–387.

Jenkins, R. R. 1993 Exercise, oxidative stress, and antioxidants: a review. *Int. J. Sports. Nutr.* **3**, 356–375.

Jones, D. B., Coulson, A. F. & Duff, G. W. 1993 Sequence homologies between hsp60 and autoantigens. *Immunol. Today* **14**, 115–118.

Kapcala, L. P., Chautard, T. & Eskay, L. R. 1995 The protective role of the hypothalamic–pituitary–adrenal axis against lethality produced by immune, infectious and inflammatory stress. *Ann. NY Acad. Sci.* **771**, 419–437.

Klasing, K. C., Laurin, D. E., Peng, R. K. & Fry, D. M. 1987 Immunologically mediated growth depression in chicks: influence of feed intake, corticosterone and interleukin. *J. Nutr.* **117**, 1629–1637.

Lamb, J. R., Bal, V., Rothbard, J. B., Mehlert, A., Mendez-Samperio, P. & Young, D. B. 1989 The mycobacterial stress protein: a common target of T-cell recognition in infection and autoimmunity. *J. Autoimmun.* **2** (Suppl.), 93–100.

Levins, R. 1968 *Evolution in changing environments*. Princeton University Press.

Locke, M. & Noble, E. G. 1995 Stress proteins: the exercise response. *Can. J. Appl. Physiol.* **20**, 155–167.

McEwen, B. S. *et al.* 1997 The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. *Brain Res. Rev.* **23**, 79–133.

Marsh, J. A. 1996 The integration of the neuroendocrine and immune systems: a marriage of convenience or necessity? In *Poultry immunology* (ed. T. F. Davison, T. R. Morris & L. N. Payne), pp. 357–374. Oxfordshire: Carfax Publishing Company.

Masman, D., Dijkstra, C., Daan, S. & Bult, A. 1989 Energetic limitation of parental effort: field experiments in the kestrel (*Falco tinnunculus*). *J. Evol. Biol.* **2**, 435–455.

Munck, A. & Náray-Fejes-Tóth, A. 1995*a* Glucocorticoids and stress: permissive and suppressive actions. *Ann. NY Acad. Sci.* **774**, 115–130.

Munck, A. & Náray-Fejes-Tóth, A. 1995*b* Glucocorticoid action: physiology. In *Endocrinology* (ed. L. J. DeGroot and others), pp. 1642–1656. Philadelphia, PA: W. B. Saunders.

Munck, A., Guyre, P. M. & Holbrook, N. J. 1984 Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr. Rev.* **5**, 25–44.

Nieman, D. C. & Nehlsen-Cannarella, S. L. 1994 The immune response to exercise. *Semin. Hematol.* **31**, 166–179.

Ornatsky, O. I., Connar, M. K. & Hood, D. A. 1995 Expression of stress proteins and mitochondrial chaperonins in chronically stimulated muscle. *Biochem. J.* **311**, 119–123.

Richner, H., Christie, P. & Oppliger, A. 1995 Paternal investment affects prevalence of malaria. *Proc. Natn. Acad. Sci. USA* **92**, 1192–1194.

Rose, N. R. & Mackay, I. R. 1992 The immune response in autoimmunity and autoimmune disease. In *The autoimmune diseases*, vol. II (ed. N. R. Rose & I. R. Mackay), pp. 1–26. Academic Press.

Sapolsky, R. M. 1992 Neuroendocrinology of the stress response. In *Behavioural endocrinology* (ed. J. B. Becker, S. M. Breedlove & D. Crews), pp. 287–324. Cambridge, MA: MIT Press.

Sheldon, B. C. & Verhulst, S. 1996 Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. *Trends Ecol. Evol.* **11**, 317–321.

Svensson, E., Råberg, L., Koch, C. & Hasselquist, D. 1998 Energetic stress, immunosuppression and the costs of an antibody response. *Funct. Ecol.* (In the press.)

Theofilopoulos, A. N. 1995 The basis of autoimmunity. I. Mechanisms of aberrant self-recognition. *Immunol. Today* **16**, 90–98.

Vehrencamp, S. L., Bradbury, J. W. & Gibson, R. M. 1989 The energetic cost of display in male sage grouse. *Anim. Behav.* **38**, 885–896.

Wedekind, C. 1992 Detailed information about parasites revealed by sexual ornamentation. *Proc. R. Soc. Lond.* B **247**, 169–174.

Wedekind, C. & Følstad, I. 1994 Adaptive or nonadaptive immunosuppression by sex hormones? *Am. Nat.* **143**, 936–938.

Wegmann, T. G., Lin, H., Guilbert, L. & Mosmann, T. R. 1993 Bidirectional cytokine interactions in the maternal–fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol. Today* **14**, 353–356.

Weight, L. M., Alexander, D. & Jacobs, P. 1991 Strenuous exercise: analogous to the acute-phase response? *Clin. Sci.* **81**, 677–683.

Westneat, D. F. & Birkhead, T. R. 1998 Alternative hypotheses linking the immune system and mate choice for good genes. *Proc. R. Soc. Lond.* B **265**, 1065–1073.

Wick, G., Hu, Y., Schwarz, S. & Kroemer, G. 1993 Immunoendocrine communication via the hypothalamo–pituitary–adrenal axis in autoimmune diseases. *Endocr. Rev.* **14**, 539–563.

Williams, G. C. 1966 Natural selection, the costs of reproduction, and a refinement of Lack's principle. *Am. Nat.* **100**, 687–690.

Williams, G. C. 1992 *Natural selection: domains, levels, and challenges*. Oxford University Press.

Winfield, J. B. & Jarjour, W. N. 1991 Stress proteins, autoimmunity, and autoimmune disease. *Curr. Top. Microbiol. Immunol.* **167**, 161–189.

Woods, J. A., Davis, J. A., Mayer, E. P., Ghaffar, A. & Pate, R. R. 1993 Exercise increases inflammatory macrophage antitumour cytotoxicity. *J. Appl. Physiol.* **75**, 879–886.

Zuk, M. 1994 Immunology and the evolution of behaviour. In *Behavioural mechanisms in evolutionary ecology* (ed. A. R. Leslie), pp. 354–368. The University of Chicago Press.