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Feature Article

Testosterone-Mediated Immune Functions and Male Life Histories

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ABSTRACT Recent advances in human life history theory have provided new insights into the potential selection pressures that were instrumental in the evolution of human and non-human primate males. However, gaps remain in our understanding of how primate males regulate and allocate energetic resources between survivorship and reproductive effort. Defense against parasitic infection is an important force shaping life history evolution. Proper performance of immunological responses against infection is influenced by many physiological systems, including metabolic, reproductive, and stress hormones. Because androgens influence and modulate immune, reproductive, and somatic metabolic functions, assessing changes in testosterone and immune factors during infection may yield insight into male physiological ecology. In this review, we examine male life history trade-offs between immune and reproductive endocrine functions as well as provide a comprehensive review of testosterone–immunocompetence relationships. Emphasis is placed on testosterone because it is a primary hormone shown to be crucial to energy-allocation processes in vertebrates. Non-primate species have been used more extensively in this research than humans or non-human primates, and therefore this extensive literature is organized and reviewed in order to better understand potential parallel relationships in primates, especially humans. Furthermore, we attempt to reconcile the many inconsistent results obtained from field studies on immune–endocrine interactions as well as detail various methodologies that may be used to forward this research in evolutionary anthropology. Am. J. Hum. Biol. 17:527–558, 2005.

I. INTRODUCTION

The evolution of human and non-human primate life histories has been of growing interest to biological anthropologists (Bentley, 1999; Hill, 1993; Kaplan et al., 2000). While human female reproductive ecology has been studied extensively in recent years (Ellison, 1990, 1994, 2001a, b; Ellison et al., 1993;), males have come to the attention of researchers as the result of emerging data indicating reproductive endocrinological sensitivity to environmental factors such as energetic stress (Bribiescas, 1996, 2001a, b; Campbell and Leslie, 1995). Nonetheless, several important issues about male reproductive ecology remain unresolved, notably including the impact of immunological stress on the evolution of male life histories (Campbell et al., 2001; McDade, 2003).

Research on immunological stress has traditionally focused on defense against pathogens and on the direct effects of infection on morbidity and mortality. A comprehensive review of mammalian immune function is beyond the scope of this essay. Rather, we discuss the important role that immune function has played in the evolution of male life histories. In doing so, we review testosterone's actions on reproductive and immune functions. Testosterone is intimately involved in the regulation of somatic energy-resource allocation in humans and other vertebrate males (Bribiescas, 1996, 1997, 2001a, b; Marler and Moore, 1988). In fact, the use of endocrine assessment to quantify and analyze reproductive effort has met with great success in a variety of vertebrates (Ketterson

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and Nolan, 1992; Marler and Moore, 1988), including humans (Ellison, 2003). In human males in particular, testosterone appears to largely regulate energy allocation by altering anabolically sensitive tissue, including skeletal muscle mass. However, the role of testosterone in regulating energetic resources also extends to the immune system, which is energetically costly to maintain and activate. Immunological responses generate a significant energetic demand that is subject to allocation mechanisms (Muehlenbein, 2004a; Owens, 2002; Raberg et al., 1998; Schmid-Hempel, 2003; Sheldon and Verhulst, 1996). By suppressing immune responses and augmenting anabolic processes, testosterone may therefore act as a physiological mechanism regulating the relative amount of energy invested into either reproductive effort (i.e., muscle mass) or immunocompetence according to available energy and disease risk in the environment.

Here we present detailed reviews of male life history trade-offs and testosterone–immunocompetence relationships, drawing primarily from the non-primate literature as such taxa have been investigated much more extensively in this regard. This information is reviewed in the hope that human biologists and anthropologists will develop novel methods of assessing the role of immunological energetic regulation on the evolution of the primate lineage. Furthermore, this review was conducted in an effort to begin to reconcile the many inconsistent results obtained from field studies on immune-endocrine interactions as well as detail various methodologies which may be used to assess the relationship and interactions between reproductive hormones and immunological functions, which may ultimately forward this research within evolutionary anthropology.

II. TESTOSTERONE AND MALE LIFE HISTORIES

Life history theory serves as a powerful tool for describing the entire life span of an organism, and the elements of demography, quantitative genetics/reaction norms, lineage-specific effects, and trade-offs combine to help explain life history variation (Stearns, 1992). Life history theory predicts that selection will favor physiological mechanisms that efficiently regulate the allocation of energy and time between four general competing functions: reproduction, maintenance, storage, and growth (Hill, 1993; Kaplan et al., 2000; Stearns, 1992). Because energy used for one purpose cannot be used for another, organisms often face energetic trade-offs, especially under conditions of resource restriction. However, awareness is necessary for the potential existence of phenotypic correlations between competing adaptive traits (Stearns, 1992).

Among the many potential trade-offs, reproductive effort and survivorship are among the most important aspects of male and female life histories that have been subject to selection. Reproductive effort refers to the costs of both time and energy in reproductive investments. Males and females differ in the amount of time and energy they invest into reproductive effort. For mammals, this is the result of contrasting offspring investment requirements that stem from internal gestation. Although males do not undergo menstruation, gestation, childbirth, or lactation, male reproductive effort includes mate attraction, conspecific competition, mate and offspring protection and provisioning, and physiological investments in spermatogenesis and somatic tissues.

Reproductive effort and survival is a common trade-off in males and is central to iteroparous organisms because resources can be budgeted over a number of reproductive events throughout the lifespan of the organism. Physiological parameters associated with greater mate access and, occasionally, male fertility reflect this trade-off. For example, shifting investment between survivorship and reproductive effort occurs in *Drosophila* and *Caenorhabditis elegans* (Gems and Riddle, 1996; McKean and Nunney, 2001; Partridge and Farquhar, 1981). Metabolic investment in spermatogenesis can decrease survivability among certain species (Olsson et al., 1997; van Voorhies, 1992). In contrast to reptiles and invertebrates, metabolic investment in mammalian spermatogenesis is negligible, accounting for less than 1% of basal metabolic rate in human males (Elia, 1992a, b). The minor metabolic costs of spermatogenesis are clearly evident by the robustness of sperm production in humans, even under taxing energetic circumstances (Bagatell and Bremner, 1990). Therefore, one would expect minimal selection for sensitivity to energy balance on spermatogenesis (Bribiescas, 2001a, b). Nonetheless, mammals and other vertebrates exhibit altera-

tions between physiological reflections of survivorship and reproductive effort. An important metabolic trade-off in many vertebrates is between sexually dimorphic muscle mass, a reflection of somatic investment in reproductive effort, and survivorship such as adipocyte deposition (Bribiescas, 2001a, b) or increased tissue and organ maintenance or immunocompetence.

Within humans, a significant amount of population variation in testosterone is clearly evident. Salivary testosterone levels among forager, horticultural, and pastoral populations in South America (Beall et al., 1992; Bribiescas, 1996), Africa (Bentley et al., 1993; Campbell et al., 2003; Christiansen, 1991; Ellison et al., 1989; Lukas et al., 2004), and Asia (Ellison and Panter-Brick, 1996) are significantly lower than in more industrialized populations in the United States and Europe. The source of this variation remains to be fully elucidated, but it is likely that ecological differences that result in population variation in energetic status exert developmental effects (Bribiescas, 2001), likely during adolescence, that affect Leydig cell sensitivity to luteinizing hormone (LH) stimulation (Spratt and Crowley, 1988).

In addition, there is a broad range of variation in age-related changes in testosterone levels. While American males tend to exhibit a 1% decline after the age 40 (Gray et al., 1991; Harman et al., 2001), other populations are characterized by a more modest decline or no decline at all (Ellison et al., 2002). Interestingly, estradiol and gonadotropin (LH and FSH) levels exhibit much less variation in relation to ecological differences between populations. Among Ache men of Paraguay, salivary estradiol levels were unrelated to age while LH and FSH were positively associated with age, similar to what is seen in industrialized populations (Bribiescas, 2005).

Testosterone variation may reflect a somatic trade-off between reproductive effort and survivability in male mammals and other vertebrates (Bribiescas, 1997, 2001a, b). The effects of testosterone on somatic tissue composition in humans have been well documented. Testosterone and other androgens stimulate muscle anabolism by increasing protein synthesis and glucose uptake (Bhasin et al., 1996; Tsai and Sapolsky, 1996). In addition, testosterone increases metabolic rates in muscle cells in vitro (Tsai and Sapolsky, 1996), as well as in vivo. For example, 3 months of testosterone administration resulted in increased weight due to greater lean body mass, decreases in adiposity, and increases in basal metabolic rate (BMR) in control men as well as muscular dystrophy patients (Welle et al., 1992). In addition to anabolic effects, testosterone stimulates fat catabolism and adipose tissue redistribution (Marin et al., 1992a, b; Welle et al., 1992).

This implies that testosterone variation between populations, as well as the acute response of the hypothalamic–pituitary–testicular system to negative energy balance, reflects a somatic trade-off between reproductive effort and survivability and an adaptive mechanism to decrease metabolic costs in light of energy deficits (Bribiescas, 1996, 1997, 2001a, b). The hypermetabolic effects of testosterone on human male mortality are not known; however, increases in testosterone levels in other vertebrates result in greater fat catabolism, increased energetic costs, and compromised survivability (Ketterson et al., 1992; Marler and Moore, 1988; Marler et al., 1995). Other costs of testosterone which may compromise survivability include increased risk of prostate cancer (Soronen et al., 2004), production of oxygen radicals (Zirkin and Chen, 2000), and a general increased risk of injury due to hormonally augmented behaviors such as aggression, violence, and risk taking (Dabbs, 1990, 1996; Wilson and Daly, 1985).

In total, the implications of these investigations on *mammalian* male reproductive endocrine function are that metabolic investment in gametogenesis is minimal and that remaining energetic investment is available for various aspects of somatic development. Allocation decisions between somatic tissues such as skeletal muscle and adipose tissue result in contrasting investment in survivorship or reproductive effort. Bribiescas (1996, 1997, 2001a, b.) has argued that reproductive effort in human males includes not only the minimal costs of spermatogenesis but also the somatic investment of androgenic sensitive tissue, such as skeletal muscle mass. Therefore, augmentation of the ability to grow skeletal muscle reflects investment in reproductive effort, although increased metabolic costs may compromise survivorship. Investment in relatively inexpensive adipose tissue augments survivorship but may not increase competitive ability as muscle mass would (Bribiescas, 1996, 1997, 2001a, b).

However, the relationship between testosterone and anabolically sensitive tissue, such as sexually dimorphic skeletal muscle, only partially accounts for the energetic management issues faced by males. Immunocompetence, or the ability to mount an effective immune response, is also an integral part of male life histories, as detailed below.

III. IMMUNOCOMPETENCE

A. Basic Mammalian Immune Responses

A detailed discussion of testosterone-mediated immunity and its role in male life histories first requires a basic introduction to immunological terminology as well as an introductory description of the mammalian immune responses. The mammalian immune system is usually organized into two main components: innate (or constitutive) and adaptive (or acquired) immunities (Stanley, 2002). Innate immunity consists of primary mechanisms that block or eliminate foreign particles from invasion of the host. Such defenses can include anatomical barriers (mucus, skin), resident flora (nonpathogenic bacteria), humoral factors (lysozyme, complement system), and cells (phagocytes, natural killer cells, eosinophils) (Stanley, 2002). Macrophages, a major part of innate immunity, are mononuclear phagocytes that perform many tasks, such as phagocytosis, cytokine secretion, chemotaxis, and antigen processing and presentation (Miller and Hunt, 1996). The complement system is part of the innate, inflammatory response and functions to eliminate microorganisms by promoting entry of immune cells into sites of infection, lysing bacterial cells, and mediating phagocytosis (Carroll, 1998).

In adaptive immunity, effector mechanisms allow fast secondary responses during subsequent exposures. Lymphocytes, which are involved in adaptive immunity, come in two main forms: B cells and T cells (Stanley, 2002). B cells represent humoral immunity. When exposed to an antigen, activated B cells differentiate into memory cells, which function in immunosurveillance, and plasma cells, which secrete antibodies or "immunoglobulins." Antibodies neutralize pathogens and their products, induce complement activation, promote cellular migration to sites of infection, and enhance phagocytosis, among other actions (Black, 2002a; Sorensen, 2002a). Some of the most important immunoglobulins include IgG, IgM, IgA, and IgE. In general, IgG neutralizes bacteria and their toxins; IgM activates the complement cascade; IgA protects mucosal surfaces from infection; and IgE functions to clear helminth infections (Wallace Taylor, 2002).

T cells represent cellular immunity. Cytotoxic T cells ($CD8^+$) destroy infected host cells, and helper T cells ($CD4^+$) secrete cytokines (Berke, 1997; Stanley, 2002). Cytokines, secreted by both macrophages and T cells, are the "hormones of the immune system" (Sorensen, 2002b; p. 82) or glycoproteins that perform a variety of functions such as regulation of cell growth and development and other "processes leading to the restoration of homeostasis" (Burger and Dayer, 2002; p. 465). Cytokines have several striking features; most importantly, they perform pleiotropic actions and interact in different complex ways with each another (Turnbull and Rivier, 1999).

$CD4^+$ helper T cells are differentiated into two subsets: Th-1 and Th-2 phenotypes (Coffman and Mosmann, 1991; Mosmann, 1991a, b; Mosmann and Coffman, 1989a, b; Mosmann et al., 1986; O'Garra, 1998; Reiner and Seder, 1999). The type and concentration of antigen and cytokines present determine which phenotype becomes prevalent within the microenvironment (Hickey and Wallace Taylor, 2002). Low concentrations of antigen tend to stimulate the production of Th-2 cells, whereas high concentrations of antigen tend to induce Th-1 cell production (Hickey and Wallace Taylor, 2002). Th-1 cytokines include, among others, IFNγ, TNFα, IL-2, IL-3, and IL-12, which activate leukocytes and cellular immunity (T cells) (Hickey and Wallace Taylor, 2002). Th-2 cytokines include, among others, IL-4, IL-5, and IL-10, which induce humoral immunity (B cells) (Hickey and Wallace Taylor, 2002; Urban et al., 1992). Th-1 and Th-2 cytokines act antagonistically (i.e., IL-4 and IL-10 inhibit IL-12 and IFNγ activity) (O'Garra, 1998), and although both types of cytokines are usually present within the host at any given time, during infection one phenotype usually predominates.

These effector mechanisms of the mammalian immune responses function in concert, acting to limit pathogen entry and replication. However, no two parasites elicit the same immune response. Thus, each type of parasite must be considered separately when describing the immune responses (Cox, 2002). Extracellular pathogens, such as para-

sites or bacteria, tend to be cleared by a combination of phagocytes, the complement cascade, and antibodies (Rothwell, 1989; Stanley, 2002; Urban et al., 1992). In contrast, intracellular pathogens, such as viruses, are eliminated by destruction of infected host cells by cytotoxic T cells and natural killer cells (Berke, 1997; Stanley, 2002). A few examples of these different processes are discussed below.

The immune responses to parasitic infection are complex. Macrophages activated by IFNγ can phagocytose small parasites and eliminate them via toxic reactive oxygen intermediates and nitric oxide (Cox, 2002; James, 1995). These chemicals can also be secreted to eliminate larger parasites (James, 1995). In addition, antibodies can block binding to host cells (Targett, 1990) and activate the complement cascade in an attempt to eliminate the parasite. Malaria is caused by a parasite (*Plasmodium* sp.) that has both extra- and intracellular stages in its life cycle, and it elicits a complex immune response. In response to the extracellular sporozoite and merozoite stages, B cells secrete antiparasite antibodies, and phagocytes attempt to phagocytose the parasites. Phagocytes also attack infected red blood cells. Protection against *Plasmodium* basically requires the efforts of both Th-1 and Th-2 responses (Zhang et al., 2000). For example, IFNγ produced by Th-1 cells inhibited parasitemia during *Plasmodium chabaudi* infection (Stevenson et al., 1990). At the same time, TNFα is a disease-mediating cytokine in malaria and was positively correlated with greater intensity of clinical disease (Karunaweera et al., 1998).

The immune responses to intestinal parasites are equally complex. Parasitic helminths, members of the phyla Nematoda and Platyhelminthes, are cleared by Th-1 and Th-2 cytokines, antibodies, and leukocytes (Cox and Liew, 1992; King and Nutman, 1992; Rothwell, 1989; Sher and Coffman, 1992). IFNγ-activated macrophages produce high levels of nitric oxide, which is toxic to a variety of intestinal parasites. Nitric oxide induction by the intestinal epithelium also limits parasite attachment to the gastrointestinal tract (Kasper and Buzoni-Gatel, 2001). Both Th-1 cytokines (e.g., IL-1, TNFα, and IFNγ) and Th-2 cytokines (e.g., IL-4, IL-10, IL-13) function as chemoattractants for leukocytes, contributing to gut inflammation (Kasper and Buzoni-Gatel, 2001; King and Nutman, 1992; Sher and Coffman, 1992). The Th-2 response, however, seems to be mainly responsible for controlling intestinal nematode infections (Urban et al., 1992), stimulating eosinophilia, IgE, goblet cell hyperplasia, mucin production, and intestinal mastocytosis (resulting in histamine release) (Allen and Maizels, 1996; Barrett et al., 1988; Else and Finkelman, 1998; King and Nutman, 1992; MacDonald et al., 2002).

Extracellular bacterial infections are usually controlled via phagocytosis, complement activation, and IgG antibodies. IgA also blocks attachment of bacteria to mucosal surfaces. Intracellular bacteria are also controlled via antibody-dependent cell cytotoxicity and macrophage activation (Dugan, 2002). Likewise, viral infections are eliminated by multiple types of immunological responses. Natural killer cells and cytotoxic T cells ($CD8^+$), activated by antibodies and the complement cascade, can lyse infected cells (Lertmemongkolchai et al., 2001). Antibodies can also eliminate extracellular viruses and block cell entry (Lairmore, 2002).

B. Energetics of Immune Functions

It is important to clarify that the utilization of many if not all of the above-mentioned immune responses imposes an encompassing stress that can be described as an energetic burden (Muehlenbein, 2004a; Owens, 2002; Raberg et al., 1998; Sheldon and Verhulst, 1996; Schmid-Hempel, 2003). Prolonged energy and protein restriction can lead to decreased cell-mediated immunity, decreased complement-mediated immune function (Ulijaszek, 1990), inhibition of antibody production and secretion (Frisancho, 1993), reduced CD and NK cell counts and lymphocyte proliferation (Shephard et al., 1998), and downregulation of the expression of Th-2 cytokines (Ing et al., 2000; Koski et al., 1999). For example, rural Nigerian children exhibited inverse relationships between intestinal parasite infection and protein intake (Rosenberg and Bowman, 1984). Similarly, Indonesian children exhibited a positive relationship between growth stunting and intensity of *Trichuris trichiura* infection (Hadju et al., 1995). A thorough review of the intricate relationships between immune function, nutrition, and helminth infections is given by Koski and Scott (2001).

Strenuous exercise or participation in energetically demanding tasks, such as migration, breeding, or molting, can compromise immune function (Nelson et al., 2002). Deerenberg et al. (1997) have shown that only 47% of breeding zebra finches (*Taeniopygia guttata*) produced antibodies in response to infection with sheep red blood cells whereas all nonbreeding birds produced antibodies. In various avian species, increased brood size is concomitant with greater infection, most likely due to increased energetic demands in caring for a larger brood (Norris et al., 1994). Increased brood size was associated with reduced antibody response against Newcastle disease virus and increased *Haemoproteus* infection intensity in collared flycatchers (*Ficedula albicollis*) (Nordling et al., 1998), reduced antibody response against sheep red blood cells in zebra finches (*Taeniopygia guttata*) (Deerenberg et al., 1997), and increased prevalence of *Plasmodium* in male Great Tits (*Parus major*) (Richner et al., 1995). It may be the case, however, that increased parasitic prevalence in animals experiencing high levels of reproductive effort may simply result from increased contact with vectors (Norris and Evans, 2000). The cost of reproduction for any given organism will ultimately depend, in part, on the likelihood of pathogen exposure in the environment.

Various assessments of energy consumption by the immune system suggest that maintenance and stimulation of immune functions are energetically expensive (Ardwi and Newsholme, 1985; Demas et al., 1997; Lochmiller and Deerenberg, 2000; Spurlock, 1997). In one case, domestic fowl selected for a high antibody response against sheep red blood cells exhibited significantly smaller comb size than those animals selected for a low antibody response (Verhulst et al., 1999). This is currently the only study, to our knowledge, which has provided evidence for a genetic basis of the trade-off between immunocompetence and a sexual ornament, or reproductive effort in general in vertebrates. A number of studies involving invertebrates also contend that selection for resistance reduces host fecundity or competitive ability (Fellows et al., 1998; Webster and Woolhouse, 1999).

Injection of phytohemagglutinin, a mitogen that stimulates cell-mediated immune responses, resulted in a 29% increase in resting metabolic rate in the common sparrow (*Passer domesticus*), which is equivalent to the energetic expenditure needed to produce about half an egg (Martin et al., 2003). In humans, infection usually results in a 10–15% elevation in basal metabolic rate for every 1°C rise in body temperature (Elia, 1992a). Duggan et al. (1986) found that resting metabolic rate was higher in East African children during an acute episode of the measles. Likewise, Fleming et al. (1994) found that, as age increased in infants, so did the tendency of their metabolic rates to increase during signs and symptoms (not clinical diagnoses) of upper respiratory tract infections. That is, older infants exhibited acute phase responses to viral infections whereas younger infants were immature in this response (ibid.).

In general, parasitic infection is associated with increased energy consumption by host animals, and immunosurveillance and activation of the immune responses appear to be significant drains on energetic resources (Raberg et al., 1998; Verhulst et al., 1999). In addition, different immune responses (i.e., Th-1 and Th-2 lymphocyte and cytokine phenotypes) exhibit different energetic and nutritional needs which themselves can be subject to allocation mechanisms (Long and Nanthakumar, 2004). This "intra-immune allocation" could be evidenced if energy expended on the activation of one afferent mechanism to combat a certain pathogen reduced resistance to other pathogens usually controlled by other immune mechanisms (Schmid-Hempel and Ebert, 2003; Westneat and Birkhead, 1998).

C. Immunity and Male Life Histories

Immunocompetence is highly complex and energetically expensive. Given its importance in regulating differential survival between members of a population, robust immunocompetence will be highly selected for. Mate choice can enhance fitness by favoring mates that display evidence of health and well being or other advantages that may directly or indirectly increase offspring fitness (Wallace, 1891). According to Zahavi's "handicap" principle (1975), females should evaluate a male's survivability by assessing the magnitude of the surviving male's handicap or degree of attractiveness. Similarly, Hamilton and Zuk's (1982) "good genes" hypothesis contends that animals should be under selective pressure to evolve preferences for those mates that possess reli-

able indicators of pathogen resistance by scrutinizing characteristics that honestly reflect health or the ability to resist pathogens. In this case, positive correlations between a somatic attractiveness signal and immune function are hypothesized.

A number of morphological and behavioral characteristics appear to be honest sexual signals of immunocompetence in avian and other species. Tail length was positively associated with cell-mediated immune function in male blue peafowl (*Pavo cristatus*) (Moller and Petrie, 2002) and male barn swallows (*Hirundo rustica*) (Saino et al., 2002). Male barn swallows with longer outermost tail feathers also exhibited stronger primary antibody responses following an immunization (Saino et al., 2003b), had higher testosterone levels (Saino and Moller, 1994), and were preferred by females, both as social mates and extra-pair copulation partners (Saino et al., 1999). Saino and others (2002) have therefore concluded that male barn swallow tail length was under directional sexual selection.

Size of the badge (bib of feathers under the beak) in male house sparrows (*Passer domesticus*) also appears to be subject to positive directional female mate-preference (Moller et al., 1996). Badge size was indirectly associated with the size of the bursa of fabricius: birds with bigger badges were healthier than those with smaller badges. Likewise, antler development appears to be an honest signal of quality in male white-tailed deer (*Odocoileus virginianus*): antler development was negatively associated with helminth infection in male deer (Ditchkoff et al., 2001).

Songs and feather coloration are also positively associated with immunocompetence in various avian species. Male barn swallows with songs with long terminal parts exhibited higher testosterone levels, and singing rate was negatively associated with measures of immunocompetence (Saino et al., 2003a). T-cell-mediated immune response to a phytohemagglutinin injection and size of the bursa were positively correlated with song complexity in a variety of avian species, including barn swallows and dark-eyed juncos (Garamszegi et al., 2003).

Using a sample of North American fowl, Hamilton and Zuk (1982) demonstrated that bright plumage indicated genetic resistance to parasites, that females demonstrated mating preference for males with bright coloration, and that male color was an honest an indicator of offspring viability, probably through inherited disease resistance. Likewise, gape redness and saturation was positively associated with T-cell-dependent humoral immune response to injection of sheep red blood cells in nestling barn swallows (Saino et al., 2003a), and longer-tailed adult male birds had higher plasma lutein levels and brighter feather coloration (Saino et al., 1999). Male satin bowerbirds (*Ptilorhynchus violaceus*) with brighter ultraviolet plumage coloration also had lower *Haemoproteus* infections, and those males which produced higher quality bowers (elaborate twig structures) had lower ectoparasite infections (Doucet and Montgomerie, 2003).

Some primates may exhibit signals, such as coloration in facial, scrotal, and perianal regions, that reflect health or general status. However, there have been no published studies to date that have investigated relationships between immunocompetence and degree of sexual coloration in primates. On the one hand, primate male coloration and development of other secondary sexual characteristics may signal an individual's current dominance status to other males (Setchell and Dixson, 2001c). For example, adult male vervet monkeys (*Cercopithecus aethiops sabaeus*) with darker scrotal color tended to dominate males with paler scrotal color when the two animals were matched for size (Gerald, 2001). Likewise, high dominance rank in male mandrills (*Mandrillus sphinx*), geladas (*Theropithecis gelada*), and hamadryas baboons (*Papio hamadryas*) was associated with reddening of the sexual skin, brighter chest skin and prominent white capes, respectively (Dunbar, 1984; Setchell and Dixson, 2001b; Zuckerman and Parkes, 1939).

Alternatively, primate male adornment may also have evolved in response to female preference. In adult male mandrills, there exists a range of phenotypes or social variants from the "fatted" males (with intense secondary sexual coloration, large testes, and dominant positions in the social group) to "non-fatted" males (with more muted secondary sexual characteristics and non-dominant positions in the social group) (Setchell and Dixson, 2001a). Although "little is known about the attractivity of male secondary sexual adornments to females in primates" (ibid., p. 251), there is some evidence that less developed male mandrills (Setchell, 1999) and unflanged male orangutans (Rodman and Mitani, 1987) are less attractive to females. In fact, secondary sexual coloration is positively associated

with social dominance, copulatory behavior, and reproductive success in adult male mandrills (Dixson et al., 1993). It may be the case that secondary sexual coloration in this and other primate species are honest indicators of health and survivability.

In addition to the degree of development of secondary sexual characteristics, morphological asymmetry has also been viewed as a potential indicator of immunological status (Moller and Pagel, 1998). For example, fluctuating asymmetry of antlers in male reindeer (*Rangifer tarandus*) was associated with immune parameters during the rut (Lagesen and Folstad, 1998), suggesting that low fluctuating asymmetry in sexually selected ornaments may signal the ability to resist parasites. Likewise, asymmetry of non-ornamental feathers was directly associated with ectoparasite load in blackcaps (*Sylvia atricapilla*): mite infection was more intense in those with more feather asymmetry (Perez-Tris et al., 2002). Little information on this subject exists for primates, and it is uncertain whether bilateral asymmetry is an accurate indicator of immunocompetence in primates, especially humans (Moller and Swaddle, 1997). However, morphologically symmetric humans are frequently judged as more attractive and are preferred as potential mates (Gangstead and Thornhill, 1998; Grammer and Thornhill, 1994; Perrett et al. 1998). In humans, other non-physical cues may be more reliable indicators of immune status. For example, humans likely possess the ability to assess human leukocyte antigen (HLA) compatibility through olfactory means (Ober et al., 1997; Wedekind et al., 1995). More research should clearly be conducted with humans in this area.

At least in non-human species, there appear to be a number of honest physical indicators of immunocompetence. However, evidence for Hamilton and Zuk's "good genes" hypothesis is not entirely consistent: numerous studies report no relationship between parasite intensity and male mating success. Alternative explanations to that of Hamilton and Zuk may be that females choose to mate with unparasitized males just to avoid parasitic infection themselves [the "transmission avoidance hypothesis" of Borgia (1986) or the "contagion-indicator hypothesis" of Able (1996)] or to avoid mating with someone incapable of providing quality parental care [the "efficient parent hypothesis" of Milinski and Bakker (1990)]. Likewise, Thomas and others (1995) contend that the relationship between secondary sexual traits and parasite load may be mediated by age. That is, if parasitism negatively covaries with host age (possibly due to acquired immunity over time), and male brightness positively covaries with age, then females may be choosing older males which are less heavily infected (the "age-effect" hypothesis, ibid.). Thus, host age needs to be controlled for in any studies attempting to evaluate the Hamilton–Zuk hypothesis.

It does seem that female house mice can discriminate against males with major-histocompatibility (MHC) loci similar to their own (Drickamer et al., 2000; Potts et al., 1991), that female ring-necked pheasants (*Phasianus colchicus*) can increase their reproductive success by choosing mates based on spur length (von Schantz et al., 1989), and that female guppies (*Poecilia reticulata)* can assess susceptibility of males to monogenean parasites based on color patterns (Houde and Torio, 1992). However, it may just be the case that the degree of expression of a male's secondary sexual characteristic may indicate the intensity of associatively transmittable parasites, or those pathogens that can be transmitted directly to the female and her offspring via contact. Thus, female preference for healthy mates may represent selection against risk of contagious diseases (Klein and Nelson, 1999), just one of many explanations that must be kept in mind.

IV. TESTOSTERONE AS A UNIFYING LINK BETWEEN REPRODUCTION AND IMMUNITY

As discussed in Section II, testosterone variation in males likely reflects a somatic trade-off between reproductive effort and survivability and an adaptive mechanism to decrease metabolic costs in light of energy deficits. Reproductive effort in human males includes not only the minimal costs of spermatogenesis, but also the somatic investment of androgenic sensitive tissue, such as skeletal muscle mass. High testosterone levels would reflect augmentation of the ability to grow skeletal muscle or other androgen-sensitive sexually selected characteristics that enhance mate attraction and competitive ability with conspecifics for access to potential mates.

In human males, skeletal muscle tissue and brain tissue each contribute approximately 20% to basal metabolic rate (Elia, 1992a, b). However, skeletal muscle can atrophy during periods of negative energy balance (Henriksson, 1992). Thus, the cost of maintaining skeletal muscle may vary depending on environmental circumstances, and testosterone variation may be the mechanism controlling the amount of energy invested into muscle anabolism at any given time.

Maintaining high testosterone levels in order to bolster reproductive effort, such as muscle anabolism in humans, could theoretically reduce the amount of energy and/or nutrients available for energetically expensive immune responses (Muehlenbein, 2004a; Sheldon and Verhulst, 1996). That is, in addition to metabolic costs, high androgen levels could induce fitness costs by causing immunosuppression (Folstad and Karter, 1992; see Section V below) as well as diverting energy away from immunocompetence (Muehlenbein, 2004a; Wedekind and Folstad, 1994). Such costs may be expressed in increased susceptibility to infection, which would be balanced against the reproductive benefits of testosterone. Thus, testosterone's interactions with immune and reproductive functions act as important mechanisms for regulating energetic allocation between physiological needs associated with life history trade-offs, most notably, reproductive effort and survivorship (Muehlenbein, 2004a; Wedekind and Folstad, 1994) (Fig. 1).

The idea of intimate regulatory connections between the reproductive and immune systems is not a recent one. Calzolari (1889) first reported a connection between reproduction and immunology when he observed that male rabbits castrated before sexual maturity had larger thymuses than control animals. Reproductive hormones, in particular androgens with an anabolic effect, can alter immunological responses by altering antigen presentation and cellular apoptosis (Huber et al., 1999). In turn, cytokines can directly affect the hypothalamic–pituitary–testicular axis: IL-1β can suppress rat pituitary luteinizing hormone release (Bonavera et al., 1993), and both IL-1β and TNFα can decrease steroidogenic acute regulatory protein (StAR) gene expression, preventing cholesterol translocation to the mitochondrial membrane of Leydig cells, the primary source of testosterone synthesis in males (Lister and van der Kraak, 2002; Ogilvie et al., 1999). Important negative and positive feedback relationships between the immune and endocrine systems are implied by the fact that cytokine receptors have been identified on endocrine glands, and androgen receptors have been identified on T and B immune cells (Olsen and Kovacs, 1996).

With the proposition of the "immunocompetence handicap" hypothesis, Folstad and Karter (1992) were the first to formalize the concept that testosterone may balance the competing demands of increased reproductive success afforded by exaggerated secondary sexual characteristics with increased susceptibility to infection. More specifically, it was proposed that testosterone has a dual effect, stimulating the development and maintenance of secondary sexual characteristics while at the same time reducing immunocompetence (Folstad and Karter, 1992). Later, Wedekind and Folstad (1994) added that the suppression of the immune system by testosterone would allow for energy reallocation to the production of secondary sexual characteristics.

The immunocompetence handicap hypothesis adds a hormonal component to the "good genes" model of Hamilton and Zuk (1982) in that maintaining high testosterone levels is a handicap, and thus characteristics dependent upon testosterone will reflect honest indications of mate quality. However, there are a number of alternative interpretations of the immunocompetence handicap hypothesis, and thus testing it is difficult (Braude et al., 1999). Most obviously, animals with exaggerated secondary sexual characteristics or high testosterone levels should exhibit high parasite burden. In such a manner, testosterone's immunosuppressive actions would function to limit trait exaggeration and maintain honest signally through secondary sexual characteristics.

However, high testosterone levels are not always associated with immunosuppression (see below). In some cases, high-quality males exhibit high testosterone levels and low parasite loads (Zuk, 1996), suggesting a phenotypic correlation between testosterone and immunocompetence (Peters, 2000). Thus, an alternative explanation is that only those males who can withstand the immunosuppressive effects of high testosterone levels can afford to invest in secondary sexual characteristics that also depend on high testosterone levels. Lower-quality individuals cannot afford to invest in these sig-

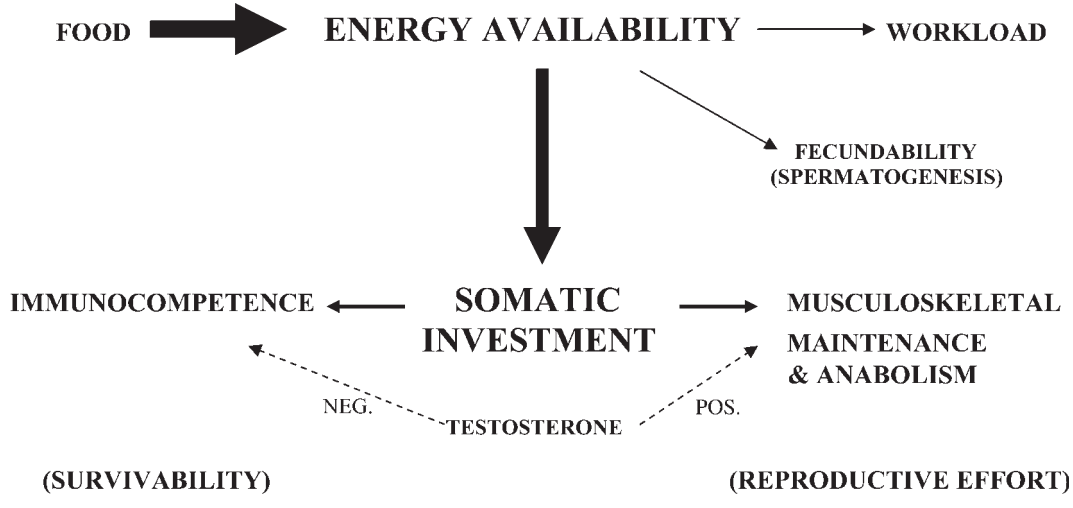

Fig. 1. Trade-off between reproductive effort and survivability (immunocompetence) in mammalian males. Although a marginal amount of investment is necessary to maintain spermatogenesis, most energetic investment is available for somatic development. Investment can be diverted to anabolic tissue such as skeletal muscle when reproductive effort is to be augmented or to immune function in order to increase survivorship.

nals because they cannot withstand the immunosuppressive effects of high testosterone levels (Evans et al., 2000; Kacelnik and Norris, 1998).

Investment in extravagant ornaments or reproductive potential in general may only be obtained via a reduction in the amount of energy invested in immunocompetence (Sheldon and Verhulst, 1996; Verhulst et al., 1999). For example, Hosken and O'Shea (2001) found a negative relationship between spleen and testis mass in two species of Australian bats, *Chalinolobus morio* and *Nyctophilus geoffroyi*. They argued that high-quality males maintain high testosterone levels and thus high spermatogenic potential and ejaculate quality, despite testosterone's immunosuppressive effects (Salvador et al., 1996; Weatherhead et al., 1993). Survival and immunity may both depend on overall condition of the organism, with those in good condition better able to invest in immunocompetence, reproduction, and survival (Sheldon and Verhulst, 1996).

The immunocompetence handicap hypothesis has not yet been evaluated in non-human primates, in part because most of these species do not exhibit obvious sexually selected characteristics. However, some species, such as mandrills (*Mandrillus sphinx*) and orangutans (*Pongo pygmaeus*), exhibit intense coloration or extreme variation in secondary sexual characteristics that appear to be under hormonal control. For example, acquiring alpha rank in adult male mandrills is accompanied by increased circulating testosterone levels and concomitant reddening of the sexual skin (Setchell and Dixson, 2001b). Likewise, development of "flanged" adult male orangutans with fully developed secondary sexual characteristics is associated with increased testosterone levels (Maggioncalda et al., 1999). Although differential infection rates or levels of immunocompetence have not been previously examined in these primate models, future analyses in these and other primate species may be insightful.

Within the adult male chimpanzees in the Ngogo community of Kibale National Park, Uganda, Muehlenbein (unpublished data) has identified significant positive associations between intestinal parasite infections, dominance rank, and testosterone levels. That is, high-ranking animals exhibited both significantly higher testosterone levels and increased intestinal parasite infections than lower-ranking animals. It is difficult to extend these results as evidence for the immunocompetence handicap hypothesis because these primates lack significant sexually selected ornaments.

The connection between testosterone, immune function, and reproductive effort may be a less obvious one in humans and other mammals that do not necessarily exhibit significant sexually selected ornaments and are characterized by intense male/male competition and more limited female choice. In this case, high testosterone levels and investment in skeletal muscle and other anabolic tissues reflects investment in reproductive effort. Energy invested into muscle anabolism is theoretically unavailable for use in mounting effective immune responses (Muehlenbein, 2004a). Furthermore, there appear to be more direct energetic connections between muscle tissue and immunity. For example, glutamine is an amino acid which is necessary for proper immune functions (Newsholme, 2001), and can become limited during overtraining (Parry-Billings et al., 1992). Furthermore, septic infection in rats reduces high-energy phosphate stores in skeletal muscle (Mizobata et al., 1995), and chronic infection with *Toxoplasma gondii* in mice reduces lipoprotein lipase activity in muscle tissues (Picard et al., 2002).

Indirect support of testosterone's modulatory effects on the trade-off between reproductive and immune functions in mammals, including humans, comes from the fact that testosterone levels and reproductive physiology frequently change with the onset of illness and somatic injury (Spratt, 2001; Spratt et al., 1993). Testicular atrophy and azoospermia are common in AIDS patients and SIV-infected non-human primates (Dym and Orenstein, 1990; Nadler et al., 1993). Serum testosterone decreases during sepsis, burns, myocardial infarction, and surgery (Spratt, 2001; Spratt et al., 1993). Experimental *Trypanosoma brucei brucei* infection in rats was associated with significant declines in serum luteinizing hormone (LH) and testosterone as well as a loss in testicular responsiveness to exogenous gonadotropin and a decline in testicular LH receptors (Soudan et al., 1992). Experimental Venezuelan equine encephalitis virus infection in captive male macaques (*Macaca fascicularis*) is also associated with significant declines in serum testosterone levels (Muehlenbein, 2004a).

In an investigation of 62 wounded soldiers in the former Yugoslavia, men with high

Injury Severity scores exhibited significantly lower testosterone levels and higher adrenocorticotropin levels, especially within the first 18 hr after being admitted for treatment compared to uninjured controls and men with war-related psychological trauma but otherwise uninjured (Cernak et al., 1997). Similarly, Honduran males infected with *Plasmodium vivax* exhibited significantly lower testosterone levels and significantly higher cortisol levels than age-matched healthy controls (Muehlenbein et al., 2005).

In addition to glucocorticoids, other factors may cause hypogonadotropism, including cytokine suppression of gonadotropin releasing hormone (GnRH) secretion, decreased stimulation of Leydig cells by luteinizing hormone (LH), increased testosterone clearance, and decreased Leydig cell responsiveness to LH (Hales, 1992; Spratt, 2001; Spratt et al., 1993). Furthermore, activated macrophages secrete nitric oxide, which at high concentrations can inhibit Leydig cell steroidogenesis (Valenti et al., 1999). Whatever the direct mechanism may be, decreased androgen production may be an adaptive response to prevent immunosuppression by high testosterone levels (Folstad and Karter, 1992) and to reallocate energy towards immune function and somatic repair (Wedekind and Folstad, 1994; Sheldon and Verhulst, 1996).

All of the hypotheses discussed above rely on two major suppositions: (1) that immunocompetence is energetically expensive, and (2) that testosterone is immunosuppressive. While the former premise is adequately supported (as detailed above in Section III, Subsection B), evidence for the latter is surprisingly mixed.

V. POTENTIAL IMMUNOSUPPRESSIVE ACTIONS OF TESTOSTERONE

Based on the theories discussed so far, it makes theoretical sense that testosterone or other anabolic steroids should possess immunosuppressive qualities. These immunoregulatory roles have been assessed mainly through four different means: (1) comparing male and female differences in immunocompetence; (2) examining associations between circulating testosterone levels and measurements of immune function, such as size of immune organs or leukocyte counts in healthy or parasitized animals; (3) experimentally manipulating testosterone levels through castration or supplementation and looking at their effects on immunocompetence; and (4) performing in vitro analyses of immune–endocrine interactions.

A. Immunocompetence in Males Versus Females

Males tend to be more susceptible to a variety of diseases, and both prevalence and intensity of infection is often higher in males than in females (Zuk and McKean, 1996). Table 1 lists the results of many of these studies. Using meta-analysis, Poulin (1996) found that males of various vertebrate taxa are more often infected with helminths than females, Moore and Wilson (2002) found that males within eight of 10 orders examined were more likely to be parasitized than females, and Brabin (1990) reported that men showed higher incidence of filarial infection than did women in 43 of 53 studies examined. Additionally, higher prevalence and intensity of parasitic infection have been reported in male reindeer (*Rangifer tarandus tarandus*) (Folstad et al., 1989), lizards (Ayala and Spain, 1976; Schall, 1996; Schall and Vogt, 1993), hamsters (Travi et al., 2002), crickets (*Acheta domesticus*) (Gray, 1998), and scorpion flies (*Harpobittacus* sp.) (Kurtz et al., 2000). Primates have been investigated much less frequently, with Fedigan and Zohar (1997) reporting increased mortality from infectious diseases in male versus female Japanese macaques (*Macaca fuscata*).

Males and females also differ in their abilities to mount effective cell- and antibody-mediated immune responses. For example, macrophage-based defenses against nematode infections are less effective in male Indian soft-furred rats (*Millardia meltada*) (Tiuria et al., 1995). Females of various species often exhibit higher levels of serum immunoglobulins (IgM, IgG, and IgA) (Kacprzak-Bergman, 1994; Lichtman et al., 1967; Olsen and Kovacs, 1996), have higher splenocyte blastogenic response to T cell mitogens (Krzych et al., 1981), and are, in general, better able to mount an antibody response to challenge than are males (Schuurs and Verheul, 1990). Females also exhibit higher $CD4^+$ helper T cell Th-2 cytokine responses (i.e., higher IL-4 and IL-10) than do males (Bijlsma et al., 1999).

TABLE 1. Studies evaluating immunocompetence in males versus females

Host species/parasite species	Study design	Outcomes	References
1. Numerous vertebrate hosts/ helminth infections	Meta-analysis	Male-biased	Poulin (1996)
2. Numerous hosts/parasites	Meta-analysis	Male-biased in 8 of 10 orders	Moore and Wilson (2002)
3. Human/filarial infections	Meta-analysis	Male-biased in 43 of 53 studies	Brabin (1990)
4. Reindeer (*Rangifer t. tarandus*)/ warble flies (*Hypoderma tarandi*)	Comparing larval abundance	Male-biased	Folstad et al. (1989)
5. Various lizard hosts/malaria (*Plasmodium*)	Infection prevalence	Male-biased	Ayala and Spain (1976); Schall and Vogt (1993); Schall (1996)
6. Hamster/*Leishmania* sp.	Comparing parasite burden	Male-biased	Travi et al. (2002)
7. Japanese macaques (*Macaca fuscata*)/ various infectious diseases	Comparing likelihood of mortality	Male-biased	Fedigan and Zohar (1997)
8. House cricket (*Acheta domesticus*)/ *Serratia liquefaciens*	Comparing susceptibility to infection	Male-biased	Gray (1998)
9. Scorpionflies (*Harpobittacus* sp.)/ various infections	Comparing susceptibility to infection	Male-biased	Kurtz et al. (2000)
10. Indian soft-furred rats (*Millardia meltada*)/ nematode infections	Macrophage activity	Less effective in males	Tiuria et al. (1995)
11. Humans and various other species	Immunoglobulin levels	Lower in males	Lichtman et al. (1967); Kacprzak-Bergman (1994); Olsen and Kovacs (1996)
12. Mice	Splenocyte blastogenic response to T-cell mitogens	Lower in males	Krzych et al. (1981)
13. Various species	Antibody responses to infection	Lower in males	Schuurs and Verheul (1990)
14. Various species	Cytokine responses	Lower in males	Bijlsma et al. (1999)
15. Numerous avian hosts/parasites	Meta-analysis	No sex differences in prevalence	McCurdy et al. (1998)
16. Mouse/*Taenia crassiceps*	Comparing susceptibility	Female-biased	Gomez et al. (2000)
17. Meadow voles (*Microtus pennsylvanicus*)	IgM responses to keyhole limpet hemocyanin	Greater response in males	Klein and Nelson (1998)
18. Great tits *(Parus major)*/*Haematozoa*	Prevalence rates	Higher in females	Norris et al. (1994)
19. Humans/various autoimmune diseases	Incidence rates	Higher in females	Da Silva (1995)

However, male biases in parasitism may not be a general rule (Schalk and Forbes, 1997). Using a meta-analysis of avian hosts (33 studies), McCurdy et al. (1998) found no overall differences in prevalence between males and females. Unexpectedly, *Haemoproteus* was more common among breeding females than breeding males (ibid.). Reversed sex differences in susceptibility to some pathogens, such as *Schistosoma mansoni* and *Taenia crassiceps*, are not well understood, but they are not uncommon. Female mice are more susceptible to *T. crassiceps* infection than are males (Gomez et al., 2000), male meadow voles mount greater IgM responses to the novel antigen keyhole limpet hemocyanin (Klein and Nelson, 1998), and parasite prevalence is higher in female Great Tits (*Parus major*) than in males (Norris et al., 1994). Human females also suffer from greater incidence of autoimmune diseases, such as rheumatoid arthritis, Addison disease, Grave disease, and systemic lupus erythematosus (Da Silva, 1995), although this is thought to be the result of estrogens hyperactivating the female immune system (Sthoeger et al., 1988).

Although even under controlled laboratory conditions males seem to be more susceptible to infection than females, several factors, such as exposure rates, social behavior, habitat, diet, *and* hormone levels may account for some of these differences. For example, sex differences in contact with either the vector, intermediate host, or infected individuals may explain sex biases in infection (Klein, 2000). Likewise, sexual dimorphism in body size may explain some sex biases in infection: the larger sex (usually the male) tends to be more heavily parasitized than the smaller sex, and this may be due to differential exposure to parasites or differential resource allocation between growth and immunity (Moore and Wilson, 2002). Additionally, androgens may promote behaviors, such as increased day ranges, that increase the likelihood of exposure to parasites in males (Wedekind and Jakobsen, 1998; Zuk, 1996). Furthermore, differences in immune function between males and females may simply reflect fundamentally different life history strategies (Rolff, 2002). If longevity is more important for female fitness whereas mating rate is more important for male fitness, then females should invest more in immunocompetence so as to increase the probability of survival relative to males (ibid.). This hypothesis is therefore more applicable to those species, such as invertebrates, which do not produce testosterone.

B. Associations Between Immunocompetence and Endogenous Testosterone Levels

Simple correlations involving testosterone levels and immunocompetence have been sought in a variety of species, and Table 2 summarizes much of this information. It is apparent that few field studies have shown consistent correlations between endogenous testosterone levels and parasitic infections or immunocompetence. For example, in rodents, Barnard et al. (1994) found that high-ranking house mice had both high testosterone levels and reduced resistance to *Babesia microti* whereas Ganley and Rajan (2001) found that *Brugia malayi* worm burden did not correlate with serum testosterone levels in mice. In voles, testosterone levels were not different between males parasitized with the nematode *Trichinella spiralis* and unparasitized males (Klein et al., 1999), and circulating testosterone levels in males and females were not related to splenocyte proliferation (Klein et al., 1997).

Among avian species, the results are as mixed. Saino and others (Saino and Moller, 1994; Saino et al., 1995) found that, in male barn swallows (*Hirundo rustica*), there was a negative association between testosterone and intestinal parasite load but no relationship between testosterone and prevalence and intensity of ectoparasitic infections. Likewise, Hasselquist and others (1999) found no effect of testosterone on antibody production in this species. In male European starlings (*Sturnus vulgaris*), Duffy and Ball (2000) identified a negative relationship between plasma testosterone levels and antibody response to keyhole limpet hemocyanin. In contrast, Weatherhead et al. (1993) found no association between testosterone and ectoparasites or endoparasites in male red-winged blackbirds (*Agelaius phoeniceus*). Weatherhead et al. (1993) suggested that "if testosterone does compromise the immune systems of red-winged blackbirds, then either the males with the highest testosterone should have had more parasites (i.e. they were trading off reproductive performance against immunity from parasites) or fewer parasites (i.e. only resistant males

TABLE 2. Studies evaluating associations between immunocompetence and endogenous testosterone levels in males

Host species/parasite species or treatment	Outcomes	References
1. Mouse/*Babesia microti*	Negative correlation between testosterone and resistance	Barnard et al. (1994)
2. Mouse/*Brugia malayi*	No correlation between testosterone and worm burden	Ganley and Rajan (2001)
3. Vole (*Microtus* sp.)/*Trichinella spiralis*	Testosterone levels did not differ between parasitized and unparasitized animals	Klein et al. (1999)
4. Vole (*Microtus* sp.)	Testosterone levels unrelated to splenocyte proliferation	Klein et al. (1997)
5. Barn swallow (*Hirundo rustica*)/ intestinal parasites	Negative correlation between testosterone and parasite load	Saino and Moller (1994)
6. Barn swallow (*Hirundo rustica*)/ ectoparasites	No association between testosterone and prevalence and intensity of infections	Saino and Moller (1994); Saino et al. (1995)
7. Barn swallow (*Hirundo rustica*)	No association between testosterone and antibody production	Hasselquist et al. (1999)
8. European starling (*Sturnus vulgaris*)/ keyhole limpet haemocyanin	Negative correlation between testosterone and antibody response	Duffy and Ball (2002)
9. Red-winged blackbird (*Agelaius phoeniceus*)/ectoparasites and endoparasites	No association between testosterone and parasite load	Weatherhead et al. (1993)
10. Human	No association between testosterone and T or B lymphocytes; positive correlation between testosterone and $CD4^+$ cell numbers; negative correlation between testosterone and IgA levels	Granger et al. (2000)
11. Human/HIV	Negative correlation between testosterone and TNFα production	Roubenoff et al. (2002)
12. Rhesus macaques (*Macaca mulatta*)	Testosterone levels highest in Fall, and IFNγ lowest in Winter	Mann et al. (2000)
13. Long-tailed macaques (*Macaca fasicularis*)/ Venezuelan Equine Encephalitis virus	Pre-exposure testosterone levels positively correlated with post-exposure viremia	Muehlenbein (2004)
14. Common chimpanzee (*Pan troglodytes schweinfurthii*)/intestinal parasites	Positive association between testosterone and intestinal parasite richness	Muehlenbein (2004)
15. Human/chest pain and spleen complaints	Testosterone predicted presence of complaints	Campbell et al. (2001)
16. Human/*Plasmodium falciparum*	Testosterone predicted resistance to parasitemia	Kurtis et al. (2001)
17. Human/*Plasmodium vivax*	Positive association between testosterone and parasitemia	Muehlenbein et al. (2005)

could afford to elevate their testosterone)" (p. 22).

Primates have been used infrequently for assessing relationships between endogenous testosterone and immunocompetence. In eight captive male rhesus macaques, Mann et al. (2000) observed that not only were testosterone levels increased in the Fall (during the onset of the mating season), but IFNγ levels were lowest in the wintertime. Muehlenbein (2004a) has found that baseline (pre-exposure) testosterone levels in captive long-tailed macaques were positively associated with their viremia levels after experimental exposure to Venezuelan equine encephalitis virus infection.

It is probable that logistical and ethical concerns regarding trapping and sampling of endangered species, especially apes, have prevented the use of wild non-human primates in studies assessing immune–endocrine interactions. However, using non-invasive fecal collection methods, Muehlenbein (2004) evaluated possible relationships between fecal steroid levels and gastrointestinal parasite infections in the world's largest habituated population of wild chimpanzees, the Ngogo community in Kibale National Park, Uganda. Both testosterone and cortisol were positively associated with total (helminth and protozoan) parasite richness (number of unique intestinal parasite species recovered from hosts' fecal samples). Future studies should involve these and other non-invasive methods (see below).

In a large sample ($N = 4415$) of healthy military men, Granger et al. (2000) found no association between testosterone and T or B

lymphocytes, although testosterone and $CD4^+$ cell numbers were positively correlated, and testosterone and IgA levels were negatively correlated. In a population of HIV-infected men, Roubenoff et al. (2002) demonstrated that serum free testosterone was inversely associated with TNFα production. Campbell et al. (2001) assessed relationships between testosterone levels and "disease categories" ("cultural interpretation of the subjective experience of illness" [p. 168]; not a clinical diagnosis) among pastoralists in Northwest Kenya. Testosterone was a marginally significant predictor of chest pain (interpreted by the authors as potential tuberculosis infection) in both nomadic and settled Turkana, and of spleen complaints (interpreted as malarial infection) among the settled, but not the nomadic population. In contrast, Kurtis et al. (2001) found that testosterone was actually a significant predictor of resistance to *P. falciparum* parasitemia in male Kenyans.

Most recently, Muehlenbein and others (2005) have assessed changes in testosterone and cortisol levels in serial samples obtained throughout recovery from *Plasmodium vivax* infection within a population of Hondurans. Testosterone levels were positively associated with *P. vivax* parasitemia. Additionally, males infected with *P. vivax* exhibited significantly lower testosterone levels than age-matched healthy controls. As discussed above, this may be an adaptive mechanism to prevent immunosuppression by high testosterone levels (Folstad and Karter, 1992) and/or to reallocate energy toward immune function and somatic repair (Sheldon and Verhulst, 1996; Wedekind and Folstad, 1994).

C. Associations Between Immunocompetence and Castration or Testosterone Supplementation

Experimenters have compared measures of immunocompetence between castrated and non-castrated animals as well as testosterone-treated and sham-treated animals. The results of many of these studies are listed in Table 3. At least two points become clear from this: (1) non-primate species, including rodents, birds, and reptiles, have been investigated almost to the exclusion of human and non-human primates; and (2) results from various studies utilizing the same host species have yielded inconsistent conclusions.

There have been very few clinical studies that have investigated the effects of testosterone supplementation on human male immune function. In one such study, Singh et al. (2002) administered varying doses (25–600 mg) of testosterone enanthate over 20 weeks to a cohort of 61 eugonadal men in order to investigate testosterone's effects on cardiovascular risk factors such as insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein (a biomarker of inflammation). Throughout the study, testosterone was not correlated with C-reactive protein (CRP) levels, nor did CRP change with testosterone treatment. However, there is really no reason to believe that testosterone would be correlated with a marker of macrophage activation (CRP) when the immune system is not necessarily activated in healthy subjects.

The same group of investigators have also examined the effects of testosterone replacement (100 mg per week) on muscle strength and body composition in hypogonadal, HIV-infected men experiencing wasting (Bhasin et al., 2000). Whereas testosterone treatment was associated with an increase in maximum voluntary muscle strength, lean body mass, and thigh muscle volume, the absolute and percentage $CD4^+$ and $CD8^+$ cell counts and plasma HIV RNA copy number did not change.

The majority of experimental studies investigating testosterone's immunosuppressive actions in vivo have yielded mixed results. Roberts and others (2004) conducted a meta-analysis on experimental studies of testosterone and immune function (mostly in birds and reptiles) in order to assess the validity of the immunocompetence handicap hypothesis. Results were mixed: testosterone-implanted males had higher white blood cell counts than control males; there was a significant association between testosterone manipulation and ectoparasite loads, but not for endoparasites; there was a significant effect of testosterone manipulation on immune factors in reptiles and birds, but not mammals (although only four species of mammals were assessed); and there was no overall effect of testosterone on immune function within the meta-analysis sample when multiple studies on the same species were controlled for (ibid.). Clearly, future projects, especially involving mammals, are warranted in order to reconcile these mixed results.

TABLE 3. Studies evaluating associations between immunocompetence and castration or testosterone supplementation

Host species (sex)	Treatment	Parasite species	Outcome	Reference
1. Rabbit	Castration	NA	Increased thymus size	Calzolari (1889)
2. Mouse	Castration	NA	Increased thymus size	Olsen et al. (1991)
3. Mouse	Castration followed by mitogen	NA	Increased antibody production and splenocyte proliferation	Schuurs and Verheul (1990)
4. Mouse	Castration followed by burn	NA	Increased cellular immunity	Messingham et al. (2001)
5. Mouse	Castration followed by trauma	NA	Increased cellular immunity	Remmers et al. (1997); Angele et al. (1998); Wichmann et al. (1997)
6. Mouse	Castration	NA	Depressed suppressor T-cell function	Weinstein and Berkovich (1981)
7. Deer mouse	Castration	NA	No effect on lymphocyte proliferation	Demas and Nelson (1998)
8. Western fence lizard	Castration	*Plasmodium mexicanuum*	No effect on infection level	Eisen and DeNardo (2000)
9. Siberian hamster	Castration followed by phytohemagglutinin	NA	Decreased lymphocyte proliferation	Bilbo and Nelson (2001)
10. Mouse (m)	Testosterone	*Plasmodium chabaudi*	Decreased proportion of $CD4^+$ cells and immunoglobulins	Benten et al. (1993)
11. Mouse (f)	Testosterone followed by zymosan and phorbol–myristate–acetate	*Plasmodium chabaudi*	Reduced capacity of peritoneal cells to generate reactive oxygen intermediates	Benten et al. (1997)
12. Soft-furred rat (f)	Testosterone	*Nipostrongylus brasilnesis*	Reduced worm expulsion	Hadid et al. (1995); Tiuria et al. (1995)
13. Mouse (m)	Testosterone	Tapeworm sp.	Increased tapeworm egg production	Folstad and Karter (1992)
14. Mouse (f)	Testosterone	*Strongyloides ratti*	Increased susceptibility	Watanabe et al. (1999)
15. Bank vole	Testosterone	*Ixodes ricinus*	Reduced acquired immune response	Hughes and Randolph (2001)
16. Wood mouse	Testosterone	*Ixodes ricinus*	Reduced acquired immune response	Hughes and Randolph (2001)
17. Sprague-Dawley rat (m)	Testosterone followed by phytohemagglutinin	NA	Suppressed skin-test response	Mendenhall et al. (1990)
18. Sand lizard (m)	Testosterone	*Ixodes* sp.	Increased tick load	Olsson et al. (2000)
19. Northern fence lizard (m)	Testosterone	Ectoparasites	Increased ectoparasite loads	Klukowski and Nelson (2001)

(Continued)

TABLE 3. Continued

Host species (sex)	Treatment	Parasite species	Outcome	Reference
20. *Psammodromus* lizard	Testosterone	*Ixodes* sp	Increased tick loads	Salvador et al. (1996)
21. Moorhen (m/f)	Testosterone	*Menopon gallinae*	Higher infestation intensity	Eens et al. (2000)
22. Greenfinch (m)	Testosterone	Sindbis virus	No effect on viremia or antibody response	Lindstrom et al. (2001)
23. European Starling (f)	Testosterone followed by tail feather plucking	NA	Suppressed tail feather regrowth	De Ridder et al. (2002)
24. European Starling (m/f)	Testosterone followed by keyhole limpet hemocyanin	NA	Suppressed antibody response	Duffy et al. (2000)
25. European Starling (m)	Testosterone followed by phytohemagglutinin	NA	Suppressed cell-mediated response	Duffy et al. (2000)
26. European Starling (f)	Testosterone	*Staphylococcus aureaus*	Higher infections	De Ridder et al. (2002)
27. Superb fairy-wren (m)	Testosterone followed by sheep red blood cells	NA	Decreased likelihood of antibody response	Peters (2000)
28. Black-headed gull	Testosterone followed by sheep red blood cells	NA	No effect on antibody response	Ros et al. (1997)
29. Veal calves	Testosterone followed by human serum albumin	NA	No effect on antibody response	Gropp et al. (1976)
30. Dark-eyed junco (m)	Testosterone	NA	Suppressed antibody- and cell-mediated immunity	Casto et al. (2001)
31. Broiler chicken	Testosterone	NA	Inhibition of macrophage phagocytosis and lymphocyte proliferation	al-Afaleq and Homeida (1998)
32. Red jungle fowl	Testosterone	NA	Decline in lymphocyte counts	Zuk et al. (1995)
33. Barn swallow	Testosterone	NA	Decline in immunoglobulin levels but no effect on total absolute leukocyte counts	Saino et al. (1995)
34. Human (m)	Testosterone	NA	No effect on C-reactive protein levels	Singh et al. (2002)
35. Human (m)	Testosterone	HIV	No effect on $CD4^+$ and $CD8^+$ cell counts or HIV RNA copy number	Bhasin et al. (2000)

D. In Vitro Experiments of Testosterone and Immune Function

Several in vitro experiments suggest that testosterone is immunosuppressive, inhibiting lymphocyte proliferation, cytokine production, and macrophage activity, and the results of many of these studies are listed in Table 4. First, androgens have the ability to bind to the reticuloendothelial cell receptors on the thymus, altering the release of thymic factors that could affect the function of effector T-lymphocytes (Mendenhall et al., 1990). Androgen interactions with the thymus should also suggest that testosterone is important for the *development* of immunocompetence. Second, androgens can also directly affect T-lymphocytes by binding to their androgen receptors on the plasma membrane or cell nucleus (Benten et al., 1999; Maurer et al., 2001; Olsen and Kovacs, 1994; Samy et al., 2000). In both manners, testosterone can alter the $CD4^+/CD8^+$ T-cell ratio in favor of $CD8^+$ cells (Olsen et al., 1991; Weinstein and Bercovich, 1981), increase $Lyt2^+$ suppressor T-cell populations (Weinstein and Bercovich, 1981), and reduce T-helper cell function (Grossman et al., 1991; Wunderlich et al., 2002). Testosterone can also induce a rapid influx in intracellular free Ca^{2+} concentration in activated T cells, which can alter T-cell function (Benten et al., 1997; Wunderlich et al., 2002). Testosterone can also reduce B-cell lymphopoiesis, affecting antibody production (Olsen and Kovacs, 1996).

The binding of testosterone to androgen receptors on T cells can influence the types and quantity of cytokines they synthesize and release. Some evidence suggests that androgens favor the development of a $CD4^+$ type-1 phenotype of peripheral lymphocytes and cytokines (Daynes et al., 1991; Giltay et al., 2000; Huber et al., 1999), which may increase susceptibility to certain infections that are cleared via the Th-2 cytokines. Alternative evidence suggests that androgens can diminish pro-inflammatory cytokine production (specifically IL-1β, TNFα, and IFNγ) by macrophages (Daynes and Araneo, 1991; Burger and Dayer, 2002; Grossman et al., 1995; Lin et al., 1996; Smithson et al., 1998; Straub and Cutolo, 2001). Testosterone can elicit a distinct pattern of gene expression in peripheral blood mononuclear cells, affecting macrophage and natural killer-cell functions (Maurer et al., 2001). Testosterone can also inhibit the expression of nitric oxide synthase in macrophages and can impair NK cell activity and the phagocytic capacity of macrophages (Chao et al., 1994, 1995; Friedl et al., 2000; Straub and Cutolo, 2001; Zhang et al., 2001).

VI. RECONCILING THE IMMUNOREGULATORY ACTIONS OF TESTOSTERONE

Results from a number of studies suggest that testosterone may actually have beneficial

TABLE 4. In vitro experiments of testosterone and immune function

Effects of testosterone	References
1. Alter T-lymphocyte function	Mendenhall et al. (1990); Olsen and Kovacs (1994); Benten et al. (1999); Samy et al. (2000); Maurer et al. (2001)
2. Alter the $CD4^+$ $CD8^+$ T-cell ratio in favor of $CD8^+$ cells	Olsen et al. (1991); Weinstein and Bercovich (1981)
3. Increase $Lyt2^+$ suppressor T-cell populations	Weinstein and Berkovich (1981)
4. Reduce T-helper cell function	Grossman et al. (1991); Wunderlich et al. (2002)
5. Alter T-cell function by inducing a rapid influx in intracellular free Ca^{2+} concentration in activated T cells	Benten et al. (1997); Wunderlich et al. (2002)
6. Reduce B-cell lymphopoiesis and affect antibody production	Olsen and Kovacs (1996)
7. Preferentially alter the development of a $CD4^+$ type-1 phenotype of peripheral lymphocytes and cytokines	Daynes et al. (1991); Huber et al. (1999); Giltay et al. (2000)
8. Inhibit the expression of nitric oxide synthase in murine macrophages	Friedl et al. (2000)
9. Impair phagocytic capacity of macrophages and inhibit nitrite release by macrophages	Chao et al. (1994); Chao et al. (1995); Straub and Cutolo (2001)
10. Diminish pro-inflammatory cytokine production by macrophages	Daynes and Araneo (1991); Grossman et al. (1995); Lin et al. (1996); Smithson et al. (1998); Straub and Cutolo (2001); Burger and Dayer (2002)

effects on the host immune system (Barnard et al., 1996, 1998; Klein and Nelson, 1998; Ros et al., 1997). Circulating testosterone levels are associated with increased resistance to some infections, such as *Taenia crassiceps* and *Schistosoma mansoni* (Eloi-Santos et al., 1992; Nakazawa et al., 1997). Testosterone can directly inhibit the fecundity of *Schistosoma haematobium* by inhibiting glutathione *S*-transferase enzymatic activity, and thus muscle tension involved in egg laying (Remoue et al., 2002).

The natural inhibitory actions of androgens to control cytokine activities may be beneficial under certain circumstances (Burger and Dayer, 2002). Excess cytokines can lead to tissue damage and death in certain circumstances such as malaria, meningitis, and rheumatoid arthritis (Beutler and Cerami, 1988; Waage et al., 1989). Testosterone may be beneficial in keeping these cytokine levels in check, or at a physiologically optimal level. Furthermore, if testosterone promotes the development of a type-1 $CD4^{+}$ helper T-cell response, then it may promote clearance of some type-1-dependent infections, such as in murine leishmaniasis (Travi et al., 2001).

Testosterone may also help to prevent certain forms of immunopathology. For example, testosterone suppresses circulating immune complexes during malarial infection, which may help prevent immunopathological effects of this disease (Coleman et al., 1982). Androgens could thus ameliorate the symptoms of some autoimmune diseases, as suggested by Raberg et al. (1998). Because heavy physical workload, as in increased reproductive effort, could lead to the formation of waste products (e.g., heat-shock proteins) that could be damaging to tissue, testosterone's immunosuppressive actions may sometimes be beneficial (ibid.).

Hillgarth et al. (1997) suggest that the immunosuppressive actions of testosterone, if they exist, may function to protect haploid spermatozoa by inhibiting the production of anti-sperm antibodies and by promoting the function of suppresser T cells. However, Penn and Potts (1998) question this hypothesis, suggesting that we should also see high sensitivity of circulating immune cells to testosterone, which we do in certain circumstances outlined above. Braude et al. (1999) offered an alternative hypothesis, labeled "immunoredistribution." They proposed that "leukocytes are temporarily shunted to different compartments of the immune system in response to testosterone," and that "redistribution is a temporary shifting of immune cells to compartments where they are likely to be more useful," such as the skin or body openings (p. 346). For example, resources could be allocated to different sites in the soma, such as the skin or muscle tissue, in anticipation of the acquisition of injury or infectious disease, or concomitant to physiological perturbation (Adamo et al., 2001; Buchanan, 2000; Kurtz et al., 2000). It seems maladaptive that testosterone would always be immunosuppressive and "if androgens are actually immunosuppressive per se, then it is difficult to understand why males cannot evolve a nonimmunosuppressive sex hormone, convert androgens into nonimmunosuppressive form, or abolish the sensitivity of immune effectors to androgens. None of these possibilities would seem to be insurmountable evolutionary steps" (Penn and Potts, 1998: p. 392). Clearly the immunoredistribution hypothesis warrants more study.

The difficulty of past studies in yielding consistent results for the hypothesis that testosterone is immunosuppressive may simply be a result of the sampling paradigms used. First, it is difficult to compare the results of studies that use different methods to assess immune function, such as parasite loads versus immunoglobulin levels (Norris and Evans, 2000). Second, comparing the results of investigations that involve different species requires caution. Differences in body size, metabolic rate, physiology, and even phylogenetically related differences may underlie the often inconsistent results. Indeed, life history allocation decisions in iteroparous endotherms, such as humans, are distinct from ectothermic and semelparous organisms, as well as those with indeterminant growth.

Third, many studies lack the desired multiple sampling procedures necessary to measure prevalence and intensity of parasitic infection accurately (John, 1997). Fourth, measurement of a single immune parameter, such as leukocyte count or immunoglobulin level, does not accurately reflect functioning of an entire system (Klein and Nelson, 1998; Norris and Evans, 2000; Schmid-Hempel, 2003; Sheldon and Verhulst, 1996; Westneat and Birkhead, 1998). Measurement of a single parasitic taxon, rather than a "parasite community," infecting a given host may also yield mixed results (Clayton, 1991). Fifth, one cannot accurately test the relationship between

testosterone and immune function in a non-disease state. Basal testosterone levels and immunocompetence may not be related when an organism is not challenged by pathogenic infection.

Sixth, whether one identifies a negative association between testosterone and immunocompetence may depend on the parasite species being examined (Clayton, 1991). It may be that testosterone is only "involved in host interactions with virulent parasites" (Saino and Moller, 1994: p. 1331). Virulence is the "capacity [of an infectious agent] to multiply rapidly in a given host in contradistinction to the capacity to multiply less rapidly but to persist more tenaciously" (Smith, 1934: p. 119). This hypothesis may explain why testosterone levels are often not associated with measures of immunocompetence during a non-disease state in the host or during a benign infection. However, just because no clinical disease is present does not mean that the infection is not invasive and deleterious at some level (Beaver et al., 1988).

Seventh, the directionality of the association between testosterone and measures of immunocompetence may depend on the diversity in genetic "quality" of the hosts used. For example, a negative association between testosterone and immunocompetence may only be evident in lower-quality individuals (Kacelnik and Norris, 1998). That is, the costs of testosterone-mediated immunosuppression may be higher in individuals of lower genetic quality. If such research was to be conducted in humans, perhaps it would require using fluctuating asymmetry (FA) as a proxy of genetic quality, and assessing testosterone–immunocompetence correlates within and between high-FA and low-FA groups.

Eighth, few studies have included analysis of other potentially immunoregulatory hormones, such as cortisol, which might mask or augment testosterone's effects. In fact, the immunomodulatory actions of glucocorticoids are more well characterized than are those of testosterone, and Turnbull and Rivier (1999) provide an extensive review of the bidirectional communication between immune function and the hypothalamic–pituitary–adrenal axis. Cortisol can inhibit inflammation (Brown, 1994; Elenkov et al., 1996; Elenkov and Chrousos, 1999; Hadley, 1996), affect cytokine production (Turnbull and Rivier, 1999), and increase monocyte apoptosis (Norbiato et al., 1997). Furthermore, cortisol is often associated with suppression of the hypothalamic-pituitary-gonadal axis (Aakvaag et al., 1978; Bambino and Hsueh, 1981; Chatterton et al., 1997; Doerr and Pirke, 1976; Sapolsky, 1995). Because cortisol can inhibit both immune function and testosterone production, any studies that attempt to assess the immunomodulatory actions of testosterone need to include measurements of cortisol levels in their analyses. It may be the case that a portion of testosterone's immunosuppressive actions reported in the literature may be attributed to glucocorticoids attenuating cellular and humoral immunity or triggering the redistribution of leukocytes (Braude et al., 1999; Munck et al., 1984).

Finally, labeling testosterone as globally immunosuppressive, as is often the case, is inappropriate. Viral, bacterial, and parasitic infections induce pathogen-specific immune responses, and thus, studies attempting to assess testosterone–immunocompetence associations must be designed to measure pathogen-specific responses. There is no reason to believe a priori that testosterone affects all aspects of the immune system equally.

VII. CONCLUSIONS AND FUTURE DIRECTIONS

Immune–endocrine interactions in vertebrate males have been the subject of intense interest by evolutionary biologists due to the important life history trade-offs that are evident in the function of various hormones and immune factors (Casto et al., 2001; Ketterson and Nolan, 1992; McDade, 2003). Investigating the immunomodulatory actions of testosterone allows greater understanding of the evolutionary significance of immune–endocrine interactions and provides a unique life-historical perspective on mammalian immune function. Because androgens influence and regulate both immune and reproductive functions, measuring changes in hormone levels and determining how they interact with immune factors may have important implications for understanding the optimization of androgenic activity (testosterone levels as well as cellular sensitivities to testosterone) under varying environmental conditions, and consequently the evolution of the life history trade-offs between reproductive and immune functions.

Here we have presented a review of the important role that testosterone plays in various evolutionary theories of male life

histories, as well as the complex nature of testosterone-immunocompetence relationships. Simply put, diversion of metabolic energy to support immune function during infection reduces the energy available for reproduction, and reproductive effort for most male mammals comes in the form of producing and maintaining adequate musculoskeletal function (skeletal muscle mass, red blood cell quantity, cortical bone density, etc.) so as to aid in mate attraction and competition with conspecifics for access to mates. Maintaining high androgen levels could have fitness costs because it may cause immunosuppression and increase morbidity and mortality. Such costs may be expressed in increased susceptibility to parasitic infection, which would be balanced against the reproductive benefits of testosterone.

With few exceptions (Bhasin et al., 2000; Brabin, 1990; Campbell et al., 2001; Cernak et al., 1997; Gould et al., 1998; Granger et al., 2000; Kurtis et al., 2001; Lunn et al., 1997; Mann and Fraser, 1996; Mann et al., 1994, 1998; Muehlenbein, 2004a, b; Muehlenbein et al., in press; Nadler et al., 1993; Roubenoff et al., 2002; Singh et al., 2002; Spratt, 2001; Spratt et al., 1993;), humans and non-human primates have been used less frequently relative to other species for assessing testosterone–immunocompetence relationships. Tables 1–3 clearly indicate the dearth of studies using human and non-human primates. This may be due, in part, to logistical and ethical difficulties in working with wild and/or endangered primate populations, or with human populations in general. However, an accurate understanding of how testosterone mediates trade-offs between reproductive and immune functions in human and non-human primates will depend upon further testing of the hypothesis that testosterone and associated anabolic activities are immunosuppressive.

This paper has attempted to provide a critical review of the available comparative literature and propose the incorporation of ideas and theories into human evolutionary anthropology that have met with great success within the general evolutionary biology community. We therefore propose that in order to move the field of human evolutionary anthropology forward, researchers should utilize similar quantitative methods in their investigations. We propose and encourage the development of research methods that involve the incorporation of both hormonal and immunological components. In light of the success of this methodology in non-human organisms, we believe this would be best suited to test the hypothesis that energetic trade-offs between reproductive function and survivorship are a central aspect of the evolution of primate life histories. Indeed, a primary motivation for this review was the relative paucity of data from humans and non-human primates. Previous research in human biology and male reproductive ecology in general, has traditionally focused on growth, reproductive function, or immune status, but has often not meshed all three. This has not been due to lack of foresight, but the result of limitations in theoretical developments, experimental design and appropriate field methods.

Future investigations should involve both correlational and manipulative studies. In either case, sampling paradigms must include procedures necessary to accurately detect and measure parasite prevalence and intensity of infection (Muehlenbein, 2005). Diverse measures of immunity, such as both type-1 and type-2 cytokines, should be assessed rather than single immune parameters (Muehlenbein et al., in press). Furthermore, as detailed in Section VI, the proper parasite species or type of infection must be chosen, cortisol levels must be controlled for in all analyses, and, ideally, differences in host genetic "quality" should be accounted for.

In correlational or field studies, non-invasive methods for the collection and processing of biological samples can be employed. For example, steroid hormone levels are detectable in saliva, urine, and feces. Furthermore, fecal samples from wild primate populations can yield information about both steroid levels and intestinal parasite infections. Information, including testosterone levels and white blood cell counts, may also be available for various other endangered species through the International Species Information System (ISIS) *Reference Ranges for Physiological Values in Captive Wildlife* (Eagan, MN).

The quantitative assessment of immunological substances is also becoming easier and more field friendly. For example, it is relatively simple to measure IgA in saliva (Lawrence, 2002). While the utility of salivary IgA as an assessment tool has limita-

tions, the development of non-invasive immunological assessments that can be used in the field continues to grow and shows great promise (Bigler et al., 2002; George and Fitchen, 1997; Kaufman and Lamster, 2002; Lawrence, 2002; Streckfus and Bigler, 2002).

In the laboratory, future manipulative studies may include assessing changes in immunocompetence, rates of susceptibility, seroconversion, or convalescence from infection following alteration of the hypothalamic–pituitary–gonadal axis (HPG) (i.e., administration of a gonadotropin releasing hormone agonist or antagonist followed by varying levels in testosterone supplementation) in non-human primates. While it is ethically unfeasible to artificially infect humans, it may be insightful to assess changes in HPG function following prophylactic treatment with live vaccines.

Thanks to the tremendous growth and use of steroid supplementation in men, there is increased potential for observing immunological responses to androgen administration. Testosterone supplementation is being evaluated for treatment of obesity (Marin et al., 1993) as well as for increasing muscle strength and quality-of-life measures in HIV-infected men (Bhasin et al., 2000). The development of male oral contraceptives also involves the experimental manipulation of endogenous androgens, and it may be useful to initiate collaborative endeavors between human evolutionary biologists and clinicians involved with the development of male oral contraceptives. Indeed, the quest for the optimal dosage of androgens in a male oral contraceptive has been a central question in clinical endocrinology and is naturally suited for studies involving the response of immune factors to various dosages of androgens to healthy men (Grant and Anawalt, 2002). Alternatively, studies may utilize the recruitment of men who are presently using hormonal supplementation that does not require a prescription, but has been shown to exert significant androgenic effects (e.g., androstenedione, "andro") (Leder et al., 2001).

In addition to assessing the immunomodulatory actions of testosterone in human models, it is also important to further elucidate the complex energetic requirements of human immune functions as well as the various mechanisms by which hypogonadism occurs in humans in response to illness and infection. Lastly, future studies should include analysis of non-androgenic hormones that reflect energetic status, such as insulin, leptin, ghrelin, and adiponectin. Each of these hormones have been shown to exert important influences on male immune and reproductive hormone function and may serve as important biomarkers of survivorship investment (Broglio et al., 2003; Meier and Gressner, 2004; Niewiarowski et al., 2000; Wauters et al., 2000). Clearly, this will be a fruitful area of research for which collaborations between immunologists, endocrinologists, and anthropologists will be necessary.

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