Adaptive Variation in Testosterone Levels in Response to Immune Activation: Empirical and Theoretical Perspectives

Michael P. Muehlenbein*

Department of Anthropology, Indiana University, Bloomington, IN

ABSTRACT: High testosterone levels reflect investment in male reproductive effort through the ability to produce and maintain muscle tissue and thus augment mate attraction and competitive ability. However, high testosterone levels can also compromise survivorship by increasing risk of prostate cancer, production of oxygen radicals, risk of injury due to hormonally-augmented behaviors such as aggression, violence and risk taking, reduced tissue and organ maintenance, negative energy balance from adipose tissue catabolism, and suppression of immune functions. Here, I briefly discuss how inter- and intra-individual variation in human male testosterone levels is likely an adaptive mechanism that facilitates the allocation of metabolic resources, particularly in response to injury, illness or otherwise immune activation. Maintaining low testosterone levels in resource-limited and/or high pathogen-risk environments may avoid some immunosuppression and suspend energetically-expensive anabolic functions. Augmenting testosterone levels in the presence of fertile and receptive mates, areas of high food resource availability, and low disease risk habitats will function to maximize lifetime reproductive success.

INTRODUCTION

There exists an enormous amount of variation in organismal life history strategies, and much of the physiological variation between and within organisms can be explained using several concepts of life history theory, most notably trade-offs and reaction norms (Stearns, 1992; Ricklefs and Wikelski, 2002). Both somatic and reproductive physiologies are evolved response systems, shaped by natural selection to adapt individuals to changing environments. This allows for a variable physiological response in which a genotype can produce a range of phenotypes (short term changes, such as acclimatization to altitude, and long-term adaptations) depending on environmental conditions (a 'reaction norm'). However, this phenotypic plasticity is limited through lineage-specific effects (canalization of certain traits) as well as trade-offs. Assuming a limited supply of energy and time, organisms are required to allocate physiological resources between a number of competing functions, particularly reproduction, maintenance (i.e., survival) and growth (Stearns, 1989). Organisms will therefore be under selection to develop and maintain physiological systems that allow the efficient allocation of resources between these functions. In a stochastic environment, those organisms that can most efficiently regulate the allocation of these resources between competing traits will likely exhibit increased lifetime reproductive success.

*Address correspondence to: Michael P. Muehlenbein, Department of Anthropology, Indiana University, Student Building 130 701 E. Kirkwood Ave. Bloomington, IN 47405; Tel: (812) 855-1041; Fax: (812) 855-4358. E-mail: mpml@indiana.edu

Under conditions of resource restriction, a trade-off between current and future reproductive effort is predicted: investments (both physiological and behavioral) in current reproductive events may negatively affect future reproductive returns (the 'cost of reproduction' argument). Suppression of current reproduction in order to increase the likelihood of successful future reproduction should function to maximize lifetime reproductive success, particularly in unpredictable and stochastic natural and social environments (Wasser and Barash, 1983). For female mammals, investment in reproduction is particularly expensive, and recent detailed studies of human reproductive ecology have clarified how female fecundity represents an adaptive reaction norm that can respond to changes in energy flux, disease, and psychological stress (Ellison, 1990; Ellison et al., 1993; Ellison, 1994; Jasienska and Ellison, 1998; Ellison, 2003; Jasienska and Ellison, 2004). On the other hand, male reproductive physiology is very different from that of females. Here, I briefly present a basic theoretical model of phenotypic plasticity in male testosterone levels (both intra- and inter-individual) along with empirical evidence for adaptive physiological variation in response to environmental stimuli, specifically those resulting in immune activation.

MALE REPRODUCTIVE EFFORT

Given the energetic investments that females must commit to reproduction, ovarian sensitivity to environmental stressors is expected. In contrast, sperm quality or quantity are relatively unaffected by even long-term, high energetic output (Bagatell and Bremner, 1990). It is logical that spermatogenesis is not particularly sensitive to energetic circumstances (Campbell and Leslie, 1995; Bribiescas, 2001) because metabolic investment in mammalian spermatogenesis is negligible, accounting for less than 1 percent of basal metabolic rate in human males (Elia, 1992).

Testosterone levels may vary according to energy balance, but only under the most taxing circumstances. For example, complete fasting decreases testosterone and hypothalamic-pituitary functioning, although these effects appear to be quickly reversible (Klibanski et al., 1981). Variation in normal or seasonal workload and exercise appears to have little effect on testosterone levels (Roberts et al., 1993; Ellison and Panter-Brick, 1996; Bribiescas, 2001). Even if energy imbalance did affect male testosterone levels, there is little evidence that this would compromise male fecundity by altering libido since variation in testosterone level is not usually associated with libido in healthy, eugonadal men (Buena et al., 1993).

More taxing aspects of male reproductive effort that may be sensitive to environmental stressors include the physiological and behavioral mechanisms involved in attracting a mate, competing with conspecifics for access to mates, and protection and provisioning of offspring and mates. In such cases, androgenic sensitive tissue (i.e., skeletal muscle mass) is a much better proxy of male reproductive effort than is spermatogenesis, and maintaining high testosterone levels can augment male reproductive success (via work capacity and sexual selection) by allocating energy towards muscle anabolism (Bribiescas, 2001) and other musculoskeletal functions (i.e., red blood cell quantity and cortical bone density). However, this is balanced against the costs of maintaining high testosterone levels, mainly

increased energetic costs and the risk of negative energy balance (Marler and Moore, 1988), increased risk of prostate cancer (Soronen et al., 2004), production of oxygen radicals (Zirkin and Chen, 2000), increased risk of injury due to hormonally-augmented behaviors such as aggression, violence and risk taking (Dabbs, 1996), reduced tissue (especially adipose) and organ maintenance, and suppression of immune functions (Muehlenbein and Bribiescas, 2005). These costs likely account for the functional significance of high variability in testosterone levels within and between individuals.

VARIATION IN TESTOSTERONE LEVELS

Testosterone levels vary enormously *within* an individual throughout his lifetime. Moment-to-moment variation is caused by the pulsatile release of gonadotropin-releasing hormone from the hypothalamus (Spratt et al., 1988). Testosterone production can be influenced by many factors, including photoperiod (Svartberg et al., 2003), environmental pollution (Selevan et al., 2000), oxygen levels (Beall et al., 1992), and diet. For example, high alcohol consumption (Muller et al., 2003), low zinc intake (Abbasi et al., 1980), and a low carbohydrate diet (Anderson et al., 1987) may all cause decreased testosterone synthesis, although Key et al., (1990) and Deslypere and Vermeulen (1984) have reported no difference in testosterone levels in omnivorous versus vegan/vegetarian (low fat) diets. Obese individuals also typically have lower testosterone levels, due in part to aromatization of testosterone into estrogens in adipose tissue (Kley et al., 1981).

Activity patterns can alter testosterone levels (Mantzoros and Georgiadis, 1995). As already mentioned, complete fasting can decrease both testosterone and gonadotropin levels (Klibanski et al., 1981). Long-term exercise can lead to reduced testosterone levels (Bagatell and Bremner, 1990), whereas short-term exercise can cause acute increases in testosterone levels (Hackney et al., 1995).

Alterations in testosterone level may be caused by a number of behavioral stimuli, such as sexual activity, competitive action, psychological stressors, and parental status. Furthermore, testosterone levels typically decline by 1 percent a year after the age forty in North American males (Harman et al., 2001), likely due to decreased Leydig cell sensitivity (Bribiescas, 2005; Bribiescas, 2006; Campbell et al., 2006a; Campbell et al., 2006b). In contrast, other populations are characterized by more modest or no declines at all (Ellison et al., 2002).

Peripheral testosterone levels may vary as a function of altered production and secretion, conversion to other hormones, uptake into tissues, and altered metabolic clearance. Estrogens, thyroid hormones, insulin, growth hormone, albumin and sex-hormone binding globulin can all alter testosterone levels. Importantly, it must also be kept in mind that the actions of testosterone depend not only on circulating concentrations, but also on receptor numbers, distribution and affinity/sensitivity.

Testosterone levels certainly vary *between* people and populations. For example, testosterone levels are higher in adult male Bangladeshi migrants to the United Kingdom compared to residents of Bangladesh (Magid, 2006), in native Aymara men in urban versus rural Bolivia (Beall et al., 1992), as well as Chinese men living in Pennsylvania versus

Beijing, China (Santner et al., 1998). Winters and others (2001) have identified higher testosterone levels in African-American men compared to Caucasian men, whereas Litman and others (2006) have found no such difference. Heald and others (2003) have found lower testosterone levels in Pakistani men compared to men of European and African-Caribbean descent, and Kehinde and others (2006) have identified lower androgen levels in Kuwaiti and Omani men compared to German, Chinese and US populations. Brets (2005) has suggested that ethnic groups living in relatively more 'extreme environments,' such as the highland populations in Western Europe, have relatively lower testosterone levels. Compared to more industrialized populations in the United States and Europe, testosterone levels are typically lower in forager, horticultural, and pastoral populations, including the Ache of Paraguay (Bribiescas, 1996), Ariaal of Kenya (Campbell et al., 2002), Aymara of Bolivia (Beall et al., 1992), Efe of the Democratic republic of Congo (Ellison et al., 1989), !Kung San of Namibia (Christiansen, 1991a; Worthman and Konner, 1987), Lese of the Democratic republic of Congo (Bentley et al., 1993), Tamang and Kami of Nepal (Ellison and Panter-Brick, 1996), Turkana of Kenya (Campbell et al., 2006a), men from Harare, Zimbabwe (Lukas et al., 2004) and the Okavango Delta of Namibia (Christiansen, 1991b). However, proper comparison between studies is not possible in the absence of identical sample collection, storage and assay methods.

It is possible that any of the above-mentioned proximate mechanisms of testosterone variation, in addition to considerable genetic effects (Ring et al., 2005), may explain some of the differences between populations and ethnic groups. Nutritional differences during development may also play an important role in 'programming' baseline testosterone secretion for later adulthood (Bribiescas, 2001). For example, chronic undernourishment permanently decreases Leydig cell sensitivity in Indian males (Smith et al., 1975). Another important factor that likely contributes to testosterone variation within and between individuals is injury, illness or otherwise immune activation.

THE ROLES OF IMMUNE ACTIVATION

Inhibited reproductive processes are common responses to injury and infection in a variety of species, including mammals, birds, invertebrates, and plants (Walker et al., 1999; Fleury et al., 2000; Tilbrook et al., 2000; Petes et al., 2003). Besides the fact that animals are less inclined to copulate with outwardly ill partners, host infection can result in gonadal pathologies (including complete castration) as well as suppressed libido (Yirmiya et al., 1995). For example, testicular atrophy and azoospermia are common in AIDS patients and SIV-infected macaques (Dym and Orenstein, 1990; Nadler et al., 1993), and infection with either *Wucheria bancrofti* or *Onchocerca volvulus* can cause testicular pathology in humans (Nelson, 1958; Iturregui-Pagnan et al., 1976).

Hypogonadism (decreased levels of hormones from the testes or ovaries) and hypogonadotropism (decreased levels of gonadotropins from the hypothalamus and pituitary glands) are common physiological responses to somatic injury. For example, in men, serum testosterone decreases during sepsis, burns, myocardial infarction, and surgery (Spratt et al., 1993;

Spratt, 2001). Spratt et al. (1993) found that patients admitted to critical care units exhibited decreased serum testosterone that varied according to severity of illness determined via Acute Physiologic and Chronic Health Evaluation II (APACHE II) scores and by survival. In an investigation of 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 eighteen hours after being admitted for treatment compared to uninjured controls and men with war-related psychological trauma but otherwise uninjured (Cernak et al., 1997). Woolf et al. (1985) also found that, within 24 hours following brain injury, elective surgery, or myocardial infarction, mean testosterone and luteinizing hormone fell by more than 50%, although in this case there was no correlation between testosterone level and degree of impairment or invasiveness.

Hypogonadism/hypogonadotropism are common responses to infection as well. HIV-infected men frequently exhibit lowered testosterone levels (Poretsky et al., 1995). Honduran men infected with *Plasmodium vivax* exhibit significantly lower testosterone levels than age-matched healthy controls (Muehlenbein et al., 2005) (figure 1). Similarly, experimental Venezuelan Equine Encephalitis virus infection in captive male macaques (*Macaca fasicularis*) is associated with significant declines in serum testosterone levels (Muehlenbein et al., 2006). Hypogonadism has also been reported in association with African sleeping sickness (*Trypanosoma brucei*) (Reincke et al., 1998), toxoplasmosis (*Toxoplasma gondii*) (Oktenli et al., 2004), schistosomiasis (*Schistosoma mansoni)* (Saad et al., 1999)

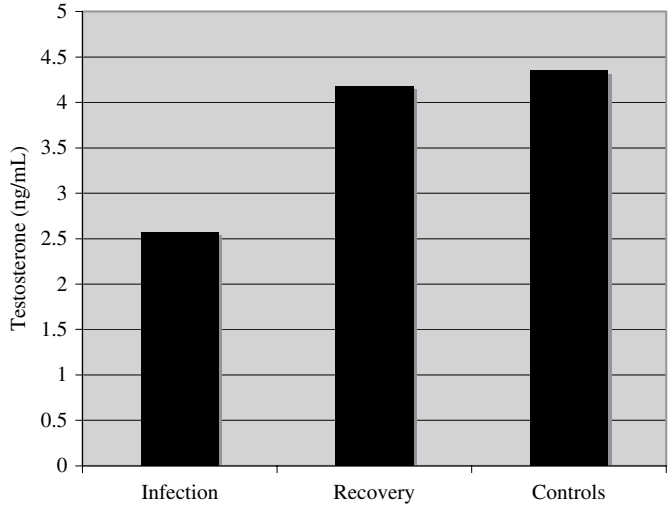

FIG. 1.—Testosterone Levels in Response to Malaria Infection.

Serum testosterone levels (ng/mL) are significantly lower in rural, Honduran men (N = 8) when naturally infected with *Plasmodium vivax* compared to their own baseline control samples (recovery samples taken approximately eight days after infection) (p = 0.016; Wilcoxon signed rank test) as well as age-matched healthy controls (N = 19) (p = 0.004; Wilcoxon rank sum exact test). Drawn from data in Muehlenbein et al. (2005).

and filarial infection (*Loa loa* and *Mansonella perstans*) (Landsoud-Soukate et al., 1989).

The proximate causes of altered androgen levels during immune activation are multifactorial. In the testes, Leydig cell production of testosterone can be altered via increased or decreased sensitivity to luteinizing hormone (LH) or through a change in numbers of LH receptors (Soudan et al., 1992; Van den Berghe et al., 1998). Activated macrophages can secrete nitric oxide, which at high concentrations can directly inhibit Leydig cell steroidogenesis (Valenti et al., 1999). Glucocorticoids like cortisol can directly suppress Leydig cell function (Gao et al., 2002; Hardy et al., 2005) and downregulate testicular LH receptors (Aakvaag et al., 1978; Bambino and Hsueh, 1981).

In the brain, glucocorticoids can directly suppress gonadotropin-releasing hormone, follicle-stimulating hormone and secretion (Attardi et al., 1997; Kalantaridou et al., 2004; Breen and Karsch, 2005). Endogenous opioids can also cause hypogonadotropism through direct effects on the hypothalamus (Sapolsky and Krey, 1988; Isseroff et al., 1989). Cytokines (especially the proinflammatory IL-1β, TNFα, and IFN-gamma) can suppress gonadotropin release from the hypothalamus and pituitary (Bonavera et al., 1993; Oktenli et al., 2004).

Although androgens, glucocorticoids and cytokines have received the most attention in regards to physiological alterations during illness/injury, assessment of other non-androgenic hormones will prove to be equally if not more insightful. For example, leptin, ghrelin, resistin and adiponectin are intimately involved in energy regulation and thus, will exert important influences on immune and reproductive functions (Niewiarowski et al., 2000; Wauters et al., 2000; Broglio et al., 2003; Meier and Gressner, 2004).

ADAPTIVE SIGNIFICANCE OF VARIATION IN TESTOSTERONE LEVELS

Similar to the adaptability of female ovarian function, changes in testosterone levels throughout the range of physiological variation may function as a basic aspect of male phenotypic plasticity and an adaptive response that facilitates the allocation of metabolic resources according to available energy and disease risk in a stochastic environment. Assuming testosterone's immunomodulatory actions are primarily suppressive (for review see Muehlenbein and Bribiescas, 2005), depressed testosterone levels during illness or injury could function to prevent immunosuppression by otherwise higher testosterone levels (Wedekind and Folstad, 1994). In addition, depressed testosterone levels could function to limit metabolic investment in energetically-expensive anabolic functions.

Skeletal muscle tissue is energetically expensive, accounting for approximately 20% of basal metabolic rate in human males (Elia, 1992), and this measure surely increases during periods of high activity. Avoiding such high costs during times of negative energy balance (or immune activation) can be accomplished through muscle atrophy and catabolism following decreased androgen levels (Henriksson, 1992). Augmenting anabolic processes through higher testosterone levels would decrease the amount of energy and nutrients available for somatic repair and the maintenance and activation of immune responses (Folstad and Karter, 1992; Muehlenbein and Bribiescas, 2005; Sheldon and Verhulst, 1996; Wedekind and Folstad, 1994).

Testosterone increases energetic costs through direct actions on muscle tissue and metabolism (Welle et al., 1992; Bhasin et al., 1996), and this may decrease survivorship in resource-limited environments (Ketterson et al., 1992; Bribiescas, 2001). The problem would become exacerbated in pathogen-rich environments because of the immunosuppressive actions of testosterone and because investment in muscle anabolism generates a significant energetic demand that will theoretically trade-off with the competing energetic demands of immunocompetence, which themselves are great (Demas et al., 2003; Raberg et al., 1998; Schmid-Hempel, 2003; Sheldon and Verhulst, 1996). Therefore, variation of testosterone level will act as a physiological mechanism regulating the differential investment in either reproductive effort (i.e., musculoskeletal performance, courtship and copulatory behaviors, etc.) or survivorship (i.e., immunocompetence, adipose tissue, etc.) according to availability of energy (Bribiescas, 2001), availability of mates (McKean and Nunney, 2005), and disease risk in the environment.

As described above, testosterone levels are determined via many factors, including diet, age and activity patterns. Certainly not all variation in testosterone levels represents an adaptive response to ecological/social stimuli. However, alterations in testosterone levels within an individual in response to illness or injury may represent an adaptive response. Disease risk, in addition to relative access to nutritional resources, may also explain some of the variation we see in testosterone levels between populations. In lower pathogen-risk environments (e.g., higher latitudes), we may hypothesize that less of a premium should be placed on immunity, and it may pay to select for less robust immune responses. In such a case, testosterone levels could theoretically be elevated (to augment reproductive effort) without incurring too much of a cost in increased morbidity and mortality from infectious diseases. In contrast, individuals inhabiting high pathogen-risk environments may benefit from decreased testosterone levels to avoid immunosuppression and suspend energetically-expensive anabolic functions. Environmental conditions, including infection, during development may ultimately play an important role in altering baseline testosterone levels as well as amount of variation experienced in adulthood. Testing such a hypothesis would require comparison of different populations from a single species subjected to different environmental constraints. Although humans are readily available research subjects, differences in genetic susceptibility and behaviors would confound such a study. Perhaps this would be best evaluated using a rodent model. Physiological variations in hormone levels in response to immune activation are important aspects of our biology that are shared with most species examined to date, and further clarifying the intricate interactions between these conserved responses will ultimately contribute to a more complete understanding of human physiological ecology.

ACKNOWLEDGEMENTS

A previous version of this paper was prepared for and presented at the International Union for the Scientific Study of Population seminar on the Ecology of the Male Life Course, October 10–12, 2006, Castle of Rauischholzhausen, Germany. Many thanks belong to Uli Mueller, Monique Borgerhoff Mulder, Hilly Kaplan and all of the IUSSP seminar participants.

REFERENCES

Abbasi, A. A., A. S. Prasad, P. Rabbani, and E. Dumouchelle. 1980. Experimental zinc deficiency in man. Effect on testicular function. J. Lab. Clin. Med. **96**:544–550.

Anderson, K., W. Rosner, M. Khan, M. New, S. Pang, P. Wissel, and A. Kappas. 1987. Diet-hormone interactions: protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. Life Sci. **40**:1761–1768.

Attardi, B., T. Toshihiko, R. Friedman, Z. Zeng, J. L. Roberts, T. Dellovade, D. W. Pfaff, U. R. Chandran, M. W. Sullivan, and D. B. Defranco. 1997. Glucocorticoid repression of gonadotropin-releasing hormone gene expression and secretion in morphologically distinct subpopulations of GT1-7 cells. Mol. Cell. Endocrinol. **131**:241–255.

Bagatell, C. J., and W. J. Bremner. 1990. Sperm counts and reproductive hormones in male marathoners and lean controls. Fertil. Steril. **53**:688–692.

Bambino, T. H., and A. J. Hsueh. 1981. Direct inhibitory effect of glucocorticoids upon testicular luteinizing hormone receptor and steroidogenesis in vivo and in vitro. Endocrinology **108**:2142–2148.

Beall, C., C. Worthman, J. Stallings, K. Strohl, G. Brittenham, and M. Barragan. 1992. Salivary testosterone concentration of Aymara men native to 3600m. Ann. Hum. Biol. **19**:67–78.

Bentley, G. R., A. M. Harrigan, B. Campbell, and P. T. Ellison. 1993. Seasonal effects on salivary testosterone levels among Lese males of the Ituri Forest, Zaire. Am. J. Hum. Biol. **5**:711–717.

Bhasin, S., T. W. Storer, N. Berman, C. Callegari, B. Clevenger, J. Phillips, R. Bunnell, A. Tricker, A. Sirzai, and R. Casaburi. 1996. The effects of supraphysiological doses of testosterone on muscle size and strength in normal men. N. Engl. J. Med. **335**:1–7.

Bonavera, J. J., S. P. Kalra, and P. S. Kalra. 1993. Mode of action of interleukin-1 in suppression of pituitary LH release in castrated male rats. Brain Res. **612**:1–8.

Breen, K. M., and F. J. Karsch. 2005. Does cortisol inhibit pulsatile luteinizing hormone secretion at the hypothalamic or pituitary level? Endocrinology **145**:692–698.

Brets, L. V. 2005. Ecological variability of hormonal concentrations in modern humans. J. Physiol. Anthropol. Appl. Hum. Sci. **24**:451–457.

Bribiescas, R. G. 1996. Testosterone levels among Ache hunter-gatherer men: A functional interpretation of population variation among adult males. Hum. Nat. **7**:163–188.

Bribiescas, R. G. 2001. Reproductive ecology and life history of the human male. Yearb. Phys. Anthropol. **44**:148–176.

Bribiescas, R. G. 2005. Age-related differences in serum gonadotropin (FSH and LH), salivary testosterone, and 17-ß estradiol levels among Ache ameridian males of Paraguay. Am. J. Phys. Anthropol. **127**:114–121.

Bribiescas, R. G. 2006. Hormones as life history regulatory agents in human males. Paper presented at the IUSSP Seminar on the Ecology of the Male Life Course.

Broglio, F., C. Gottero, E. Arvat, and E. Ghigo. 2003. Endocrine and non-endocrine actions of ghrelin. Horm. Res. **59**:109–117.

Buena, F., R. S. Swerdloff, B. S. Steiner, P. Lutchmansingh, M. A. Peterson, M. R. Pandian, M. Galmarini, and S. Bhasin. 1993. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. Fertil. Steril. **59**:1118–1123.

Campbell, B. C., and P. W. Leslie. 1995. Reproductive Ecology of Human Males. Yearb. Phys. Anthropol. **38**:1–26.

Campbell, B. C., P. W. Leslie, and K. Campbell. 2006a. Age-related changes in testosterone and SHBG among Turkana males. Am. J. Hum. Biol. **18**:71–82.

Campbell, B. C., P. W. Leslie, and K. Campbell. 2006b. Age-related patterns of urinary gonadotropins (FSH and LH) and E-3-G among Turkana males of Northern Kenya. Paper presented at the IUSSP Seminar on the Ecology of the Male Life Course.

Campbell, B. C., M. T. O'rourke, and S. F. Lipson. 2003. Salivary testosterone and body composition among Ariaal males. Am. J. Hum. Biol. **15**:697–708.

Cernak, I., J. Savic, and A. Lazarov. 1997. Relations among plasma prolactin, testosterone, and injury severity in war casualties. World J. Surg. **21**:240–245.

Christiansen, K. H. 1991a. Serum and saliva sex hormone levels in Kung San men. Am. J. Phys. Anthropol. **86**:37–44.

Christiansen, K. H. 1991b. Sex hormone levels, diet and alcohol consumption in Namibian Kavango men. Homo **42**:43–62.

Dabbs, J. M. 1996. Testosterone, aggression, and delinquency, p. 179–190, In S. Bhasin, H. L. Gabelnick, J. M. Spieler, R. S. Swerdloff, C. Wang, and C. Kelly (eds.) Pharmacology, Biology, and Clinical Applications of Androgens. Wiley-Liss, New York.

Demas, G. E., D. L. Drazen, and R. J. Nelson. 2003. Reductions in total body fat decrease humoral immunity. Proc. R. Soc. Lond. B Biol. Sci. **270**:905–911.

Deslypere, J., and A. Vermeulen. 1984. Leydig cell function in normal men: effect of age, life-style, residence, diet, and activity. J. Clin. Endocrinol. Metab. **53**:58–68.

Dym, M., and J. Orenstein. 1990. Structure of the male reproductive tract in AIDS patients, p. 181–196, In N. J. Alexander, H. L. Gabelnick, and J. M. Spieler (eds.) Heterosexual Transmission of AIDS. Alan R. Liss, New York.

ELIA, M. 1992. Organ and tissue contribution to metabolic rate, p. 51–79, In J. M. MCKINNEY and H. N. TUCKER (eds.) Energy Metabolism: Tissue Determinents and Cellular Corollaries. Raven Press, New York.

ELLISON, P. T. 1990. Human ovarian function and reproductive ecology: new hypotheses. Am. Anthropol. **92**:933–952.

ELLISON, P. T. 1994. Advances in human reproductive ecology. Annu. Rev. Anthropol. **23**:255–275.

ELLISON, P. T. 2003. Energetics and reproductive effort. Am. J. Hum. Bio. **15**:342–351.

ELLISON, P. T., R. G. BRIBIESCAS, G. R. BENTLEY, B. C. CAMPBELL, S. F. LIPSON, C. PANTER-BRICK, and K. HILL. 2002. Population variation in age-related decline in male salivary testosterone. Hum. Reprod. **17**:3251–3253.

ELLISON, P. T., S. LIPSON, and M. MEREDITH. 1989. Salivary testosterone levels in males from the Ituri Forest, Zaire. Am. J. Hum. Biol. **1**:21–24.

ELLISON, P. T., and C. PANTER-BRICK. 1996. Salivary testosterone levels among Tamang and Kami males of central Nepal. Hum. Bio. **68**:955–965.

ELLISON, P. T., C. PANTER-BRICK, S. F. LIPSON, and M. T. O'ROURKE. 1993. The ecological context of human ovarian function. Hum. Reprod. **8**:2248–2258.

FLEURY, F., F. VAVRE, N. RIS, P. FOUILLET, and M. BOULETREAU. 2000. Physiological cost induced by the maternally-transmitted endosymbiont *Wolbachia* in the *Drosophila* parasitoid *Leptopilina heterotoma*. Parasitology **121**:493–500.

FOLSTAD, I. and A. J. KARTER. 1992. Parasites, bright males and the immunocompetence handicap. Am. Nat. **139**:603–622.

GAO, H. B., M. H. TONG, Y. Q. HU, Q. S. GUO, R. GE, and M. P. HARDY. 2002. Glucocorticoid induces apoptosis in rat leydig cells. Endocrinology **143**:130–138.

HACKNEY, A. C., M. C. PREMO, and R. G. MCMURRAY. 1995. Influence of aerobic versus anaerobic exercise on the relationship between reproductive hormones in men. J. Sports Sci. **13**:305–311.

HARDY, M. P., H. B. GAO, Q. DONG, R. GE, Q. WANG, W. R. CHAI, X. FENG, and C. SOTTAS. 2005. Stress hormone and male reproductive function. Cell Tissue Res. **322**:147–153.

HARMAN, S. M., E. J. METTER, J. D. TOBIN, J. PEARSON, and M. R. BLACKMAN. 2001. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J. Clin. Endocrinol. Metab. **86**:724–731.

HEALD, A. H., F. IVISON, S. G. ANDERSON, K. CRUICKSHANK, I. LAING, and J. M. GIBSON. 2003. Significant ethnic variation in total and free testosterone concentration. Clin. Endocrinol. **58**: 262–266.

HENRIKSSON, J. 1992. Energy metabolism in muscle: its possible role in the adaptation to energy deficiency, p. 345–365, In J. M. MCKINNEY and H. N. TUCKER (eds.) Energy Metabolism: Tissue Determinents and Cellular Corollaries. Raven Press, New York.

ISSEROFF, H. P.W. SYLVESTER, C. L. BESSETTE, P. L. JONES, W. G. FISHER, T. A. RYNKOWSKI, and K. R. GREGOR. 1989. Schistosomiasis: role of endogenous opioids in suppression of gonadal steroid secretion. Comp. Biochem. Physiol. **94**:41–45.

ITURREGUI-PAGNAN, J. R., R. F. FORTUNO, and M. A. NOY. 1976. Genital manifestations of filariasis. Urology **8**:207–209.

JASIENSKA, G., and P. T. ELLISON. 1998. Physical work causes suppression of ovarian function in women. Proc. R. Soc. Lond. B **265**:1847–1851.

JASIENSKA, G., and P. T. ELLISON. 2004. Energetic factors and seasonal changes in ovarian function in women from rural Poland. Am. J. Hum. Biol. **16**:563–580.

KALANTARIDOU, S. N., A. MAKRIGIANNAKIS, E. ZOUMAKIS, and G. P. CHROUSOS. 2004. Stress and the female reproductive system. J. Reprod. Immunol. **62**:61–68.

KEHINDE, E. O., A. O. AKANJI, A. MEMON, A. A. BASHIR, A. S. DAAR, K. A. AL-AWADI, and T. FATINIKUN. 2006. Prostate cancer risk: the significance of differences in age related changes in serum conjugated and unconjugated steroid hormone concentrations between Arab and Caucasian men. International Urol. Nephrol. **38**:33–44.

KETTERSON, E. D., V. NOLAN, L. WOLF, and C. ZIEGENFUS. 1992. Testosterone and avian life histories: effects of experimentally elevated testosterone on behavior and correlates of fitness in the darkeyed junco (*Junco hyemalis*). Am. Nat. **140**:980–999.

KEY, T., L. ROE, M. THOROGOOD, J. MOORE, G. CLARK, and D. WANG. 1990. Testosterone, sex hormone-binding globulin, calculated free testosterone, and oestradiol in male vegans and omnivores. Brit. J. Nutr. **64**:111–119.

KLEY, H. K., T. DESELAERS, and H. PEERENBOOM. 1981. Evidence for hypogonadism in massively obese males due to decreased free testosterone. Horm. Metab. Res. **13**:639–641.

KLIBANSKI, A., I. A. BEITINS, T. BADGER, R. LITTLE, and J. W. MCARTHUR. 1981.Reproductive function during fasting in men. J. Clin. Endocrinol. Metab. **53**:258–263.

LANSOUD-SOUKATE, J., A. DUPONT, M. L. DE REGGI, G. E. ROELANTS, and A. CAPRON. 1989. Hypogonadism and ecdysteroid production in *Loa loa* and *Mansonella perstans* filariasis. Acta Tropica **46**:249–256.

LITMAN, H. J., S. BHASIN, C. L. LINK, A. B. ARAUJO, and J. B. MCKINLAY. 2006. Serum androgen levels in black, Hispanic, and white men. J. Clin. Endocrinol. Metab. **91**:4326–4334.

LUKAS, W. D., B. C. CAMPBELL, and P. T. ELLISON. 2004. Testosterone, aging, and body composition in men from Harare, Zimbabwe. Am. J. Hum. Biol. **16**:704–712.

MAGID, K. 2006. Bangladeshi-born adult migrants to the UK show greater salivary testosterone than sedentees. Paper presented at the IUSSP Seminar on the Ecology of the Male Life Course.

MANTZOROS, C. S., and E. I. GEORGIADIS. 1995. Body mass and physical activity are important predictors of serum androgen concentrations in young healthy men. Epidemiology **6**:432–435.

MARLER, C. A., and M. C. MOORE MC. 1988. Evolutionary costs of aggression revealed by testosterone manipulations in free-living lizards. Behav. Ecol. Sociobiol. **23**:21–26.

MCKEAN, K. A., and L. NUNNEY. 2005. Bateman's principle and immunity: phenotypically plastic reproductive strategies predict changes in immunological sex differences. Evolution Int. J. Org. Evolution **59**:1510–1517.

MEIER, U., and A. M. GRESSNER. 2004. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clinical Chemistry **50**:1511–1525.

MUEHLENBEIN, M. P., J. ALGIER, F. COGSWELL, M. JAMES, and D. KROGSTAD. 2005. The reproductive endocrine response to *Plasmodium vivax* infection in Hondurans. Am. J. Trop. Med. Hyg. **73**:178–187.

MUEHLENBEIN, M. P., and R. G. BRIBIESCAS. 2005. Testosterone-mediated immune functions and male life histories. Am. J. Hum. Biol. **17**:527–558.

MUEHLENBEIN, M. P., F. COGSWELL, M. JAMES, J. KOTERSKI, and G. LUDWIG. 2006. Testosterone correlates with Venezuelan Equine Encephalitis virus infection in macaques. Virol. J. **3**:1–5.

MULLER, M., I. DEN TONKELAAR, J. H. H. THIJSSEN, D. E. GROBBEE, and Y. T. VAN DER SCHOUW. 2003. Endogenous sex hormones in men aged 40–80 years. Euro. J. Endocrinol. **149**:583–589.

NADLER, R. D., A. D. MANOCHA, and H. M. MCCLURE. 1993. Spermatogenesis and hormone levels in rhesus macaques inoculated with simian immunodeficiency virus. J. Med. Primatol. **22**:325–329.

NELSON, G. S. 1958. 'Hanging groin' and hernia complication of onchocerciasis. Trans. R. Soc. Trop. Hyg. **52**:222–225.

NIEWIAROWSKI, P. H., M. L. BALK, and R. L. LONDRAVILLE. 2000. Phenotypic effects of leptin in an ectotherm: a new tool to study the evolution of life histories and endothermy? J. Exp. Biol. **203**:295–300.

OKTENLI C., L. DOGANCI, T. OZGURTAS, R. E. ARAZ, M. TANYUKSEL, U. MUSABAK, S. Y. SANISOGLU, Z. YESILOVA, M. K. ERBIL and A. INAL. 2004. Transient hypogonadotrophic hypogonadism in males with acute toxoplasmosis: suppressive effect of interleukin-1ß on the secretion of GnRH. Hum. Repro. **19**:859–866.

PETES, L. E., C. D. HARVELL, E. C. PETERS, M. A. H. WEBB, and K. M. MULLEN. 2003. Pathogens compromise reproduction and induce melanization in Caribbean sea fans. Mar. Ecol. Prog. Ser. **264**:167–171.

PORESTSKY, L. S. CAN, and B. ZUMOFF. 1995. Testicular dysfunction in human immunodeficiency virus-infected men. Metabolism **44**:946–953.

RABERG, L., M. GRAHN, D. HASSELQUIST, and E. SVENSSON. 1998. On the adaptive significance of stress-induced immunosuppression. Proc. R. Soc. Lond. B Biol. Sci. **265**:1637–1641.

REINCKE, M., W. ARLT, C. HEPPNER, F. PETZKE, G. P. CHROUSOS, and B. ALLOLIO. 1998. Neuroendocrine dysfunction in African trypanosomiasis. The role of cytokines. Ann. N.Y. Acad. Sci. **840**:809–821.

RICKLEFS, R. E., and M. WIKELSKI. 2002. The physiology/life history nexus. Trends Ecol. Evol. **17**:462–468.

RING, H. Z., C. N. LESSOV, T. REED, R. MARCUS, L. HOLLOWAY, G. E. SWAN, and D. CARMELLI. 2005. Heritability of plasma sex hormones and hormone binding globulin in adult male twins. J. Clin. Endocrinol. Metab. **90**:3653–3658.

ROBERTS, A. C., R. D. MCCLURE, R. I. WEINER, and G. A. BROOKS. 1993. Overtraining affects male reproductive status. Fertil. Steril. **60**:686–692.

SAAD, A. H., A. ABDELBAKY, A. M. OSMAN, K. F. ABDALLAH, and D. SALEM. Possible role of *Schistosoma mansoni* infection in male hypogonadism. J. Egypt. Soc. Parasitol. **29**:307–323

SANTNER, S. J., B. ALBERTSON, G. Y. ZHANG, G. H. ZHANG, M. SANTULLI, C. WANG, L. M. DEMERS, C. SHACKLETON, and R. J. SANTEN. 1998. Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. J. Clin. Endocrinol. Metab. **83**:2104–2109.

SAPOLSKY, R. M., and L. C. KREY. 1988. Stress-induced suppression of luteinizing hormone concentrations in wild baboons: role of opiates. J. Clin. Endocrinol. Metab. **66**:722–726.

SCHMID-HEMPEL, P. 2003. Variation in immune defence as a question of evolutionary ecology. Proc. R. Soc. Lond. B Biol. Sci. **270**:357–366.

SELEVAN, S. G., L. BORKOVEC, V. L. SLOTT, Z. ZUDOVA, J. RUBES, D. P. EVENSON, and S. D. PERREAULT. 2000. Semen quality and reproductive health of young Czech men exposed to seasonal air pollution. Env. Health Perspect. **108**:887–894.

SHELDON, B. C., and S. VERHULST. 1996. Ecological immunology: costly parasite defenses and tradeoffs in evolutionary ecology. Trends Ecol. Evol. **11**:317–321.

SMITH, S. R., M. K. CHHETRI, J. JOHANSON, N. RADFAR, and C. J. MIGEON. 1975. The pituitary-gonadal axis in men with protein-calorie malnutrition. J. Clin. Endocrinol. Metab. **41**:60–69.

SORONEN, P., M. LAITI, S. TORN, P. HARKONEN, L. PATRIKAINEN, Y. LI, A. PULKKA, R. KURKELA, A. HERRALA, H. KAIJA, V. ISOMAA, and P. VIHKO. 2004. Sex steroid hormone metabolism and prostate cancer. J. Steroid Biochem. Mol. Biol. **92**:281–286.

SOUDAN, B., D. TETAERT, A. RACADOT, P. DEGAND, and A. BOERSMA. 1992. Decrease of testosterone level during an experimental African trypanosomiasis: involvement of a testicular LH receptor desensitization. Acta Endocrinol. (Copenh.) **127**: 86–92.

SPRATT, D. I. 2001. Altered gonadal steroidogenesis in critical illness: is treatment with anabolic steroids indicated? Best Pract. Res. Clin. Endocrinol. Metab. **15**:479–494.

SPRATT, D. I., L. S. O'DEA, D. SCHOENFELD, J. BUTLER, P. N. RAO, and W. CROWLEY Jr. 1988. Neuroendocrine-gonadal axis in men: frequent sampling of LH, FSH, and testosterone. Am. J. Physiol. **254**:658–666.

SPRATT, D. I., P. COX, J. ORAV, J. MOLONEY and T. BIGOS. 1993. Reproductive axis suppression in acute illness is related to disease severity. J. Clin. Endocrinol. Metab. **76**:1548–1554.

STEARNS, S. 1989. Trade-offs in life-history evolution. Funct. Ecol. **3**:259–268.

STEARNS, S. 1992. The Evolution of Life Histories. Oxford University Press, New York.

SVARTBERG, J., R. JORDE, J. SUNDSFJORD, K. H. BONAA, and E. BARRETT-CONNER. 2003. Seasonal variation of testosterone and waist to hip ratio in men: the Tomso Study. J. Clin. Endocrinol. Metab. **88**:3099–3104.

TILBROOK, A. J., A. I. TURNER, and I. J. CLARKE. 2000. Effects of stress on reproduction in nonrodent mammals: the role of glucocorticoids and sex differences. Rev. Reprod. **5**:105–113.

VALENTI, S., C. M. CUTTICA, M. GIUSTI, and G. GIORDANO. 1999. Nitric oxide modulates Leydig cell function in vitro: is this a way of communication between the immune and endocrine system in the testis? Ann. N.Y. Acad. Sci. **876**:298–300.

VAN DEN BERGHE, G., F. DE ZEGHER, and R. BOUILLON. 1998. Acute and prolonged critical illness as different neuroendocrine paradigms. J. Clin. Endocrinol. Metab. **83**:1827–1834.

WASSER, S. K., and D. P. BARASH. 1983. Reproductive suppression among female mammals: implications for biomedicine and sexual selection theory. Q. Rev. Biol. **58**:513–538.

WALKER, N. R., T. L. KIRKPATRICK, and C. S. ROTHROCK. 1999. Effect of temperature on a histopathology of the interaction between *Meloidogyne incognita* and *Thielaviopsis basicola* on cotton. Phytopathology **89**:613–617.

WAUTERS, M., R. V. CONSIDINE, and L. F. VAN GAAL. 2000. Human leptin: from an adipocyte hormone to an endocrine mediator. Eur. J. Endocrinol. **143**:293–311.

WEDEKIND, C., and I. FOLSTAD. 1994. Adaptive or nonadaptive immunosuppression by sex-hormones. Am. Nat. **143**:936–938.

WELLE, S., R. JOZEFOWICZ, G. FORBES, and R. C. GRIGGS. 1992. Effect of testosterone on metabolic rate and body composition in normal men and men with muscular dystrophy. J. Clin. Endocrinol. Metab. **74**:332–335.

WINTERS, S. J., A. BRUSKY, J. WEISSFELD, D. L. TRUMP, M. A. DYKY, and V. HADEED. 2001. Testosterone, sex hormone-binding globulin, and body composition in young adult African American and Caucasian men. Metabolism **50**:1242–1247.

WOOLF, P. D., R. W. HAMILL, J. V. MCDONALD, L. A. LEE, and M. KELLY. 1985. Transient hypogonadotropic hypogonadism caused by critical illness. J. Clin. Endocrinol. Metab. **60**:444–450.

WORTHMAN, C. M., and M. J. KONNER. 1987. Testosterone levels change with subsistence hunting effort in !Kung San men. Psychoneuroendocrinology **12**:449–458.

YIRMIYA, R., R. AVITSUR, O. DONCHIN, and E. COHEN. 1995. Interleukin-1 inhibits sexual behavior in female but not male rats. Brain Behav. Immun. **9**:220–233.

ZIRKIN, B. R., and H. CHEN. 2000. Regulation of Leydig cell steroidogenic function during aging. Biol. Reprod. **63**:977–981.