Chapter 7
Immunity, Hormones, and Life History Trade-Offs

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Abstract Immunity is an integral part of organismal life histories because it is crucial for maximizing evolutionary fitness, and because it is energetically expensive to develop, maintain, and activate. This chapter orients the reader to the roles of immunity in human life history trade-offs, and specifically the utility of sex hormones in mediating variation in immunity. Hormones are central mechanisms that contribute to the onset and timing of key life history events, fine-tune the optimal allocation of time and energy between competing functions, and in general modulate phenotypic development and variation. Here we describe the roles of testosterone, dehydroepiandrosterone, and estradiol in moderating immunocompetence from a life history perspective, illustrating how correlated changes in immunity and gonadal function reflect the manifold interactions between these two systems. The immunomodulatory actions of these hormones are complex and varied, and we attempt to provide explanations for this variation from the literature. Although our evidence comes from clinical medicine, our basic prediction is derived from life history theory: altering the hormonal milieu may result in differential susceptibility to both infectious and chronic diseases. Furthermore, the immunological costs associated with hormone supplementation are worthy of greater consideration by both clinical practitioners and evolutionary ecologists alike.

7.1 Trade-Offs and Hormones

Life history strategies are complex adaptations for survival and reproduction that require the coordinated evolution of somatic and reproductive developmental processes (Stearns 1992). A cornerstone of life history and evolutionary theory is the importance of phenotypic plasticity, or the ability of an organism to alter its morphological, physiological, and behavioral phenotype in response to environmental change. Since environments and selection pressures can change rapidly, it is seldom adaptive for an organism to maintain a rigid set of phenotypes (Schlichting and Pigliucci 1998). Plasticity in response to stochastic ecological stressors, like the

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presence of pathogens or available mates, represents a suite of complex adaptations that are manifested in the form of reaction norms produced by natural and sexual selection, and constrained by trade-offs under conditions of resource restriction (Sinervo and Svensson 1998). Reaction norms consist of the range of phenotypes that can be produced by a given genotype through short-term changes (for example, acclimatization to high altitude), as well as long-term adaptations. Phenotypic plasticity is limited through lineage-specific effects (i.e., the canalization of certain traits; phylogenetic constraints) 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, most notably reproduction, maintenance (i.e., survival), storage, work, and growth (Stearns 1989). Organisms will therefore be under selection to develop and maintain physiological systems that allow for the efficient distribution of resources between these functions. In a stochastic environment, those organisms that can most efficiently regulate the allocation of resources between competing traits will likely exhibit increased lifetime reproductive success.

Trade-offs involving reproduction are common, particularly in iteroparous (continually reproducing) organisms like humans that must balance investments between current and future reproductive events, as well as between survival and reproduction. This is to be expected given the central role of reproduction in life history evolution. Recent studies in reproductive ecology illustrate the flexibility of human reproduction in response to energetic conditions (Bribiescas 2001; Ellison 2003). Endocrinological mechanisms sensitive to environmental cues can facilitate modulation of reproductive effort relative to other investments. Both from a macro- and a microevolutionary perspective, hormones are central mechanisms that contribute to the onset and timing of key life history events, the optimal allocation of time and energy between competing functions, and the general modulation of phenotypic development and variation (Muehlenbein and Bribiescas 2005; Bribiescas and Ellison 2008; Muehlenbein and Flinn 2011). This is particularly true for steroids, ancient lipid-soluble molecules derived from cholesterol and shared by all vertebrates. Steroid hormones are involved in modulating behavior, metabolism, growth and development, reproduction, senescence, and immune functions, among others. Complex interaction and crosstalk between different steroid hormones (and other types of hormones) are therefore implicated in many aspects of human health.

It is inherently difficult to measure life history mechanisms and quantify trade-offs in humans, since we are unable to directly manipulate the system to produce genetically evolved response patterns that clearly produce phenotypic variation cued by specific environmental signals. But, as in most other organisms examined to date, the human neuroendocrine system is undoubtedly a central mediator of our phenotypic variation, including variation in life history traits (Finch and Rose 1995). For example, testosterone can facilitate male reproductive success by modifying behaviors (i.e., competition and sexual motivation) in addition to physical attributes (i.e., spermatogenesis, muscle anabolism, and fat catabolism). Musculoskeletal function can augment work capacity, intrasexual competition, intersexual coercion, and mate choice. However, high testosterone levels could also compromise survivorship by increasing energetic costs; such costs may explain the functional significance of the high variability in testosterone levels seen within men, and within

and between populations (Bribiescas 2001; see Chap. 9 in this volume). This problem would become exacerbated in resource-limited environments.

The regulatory role of testosterone in allocating energetic resources and male reproduction also extends to the immune system. Maintaining high testosterone levels to bolster reproductive effort could reduce the amount of energy or nutrients available for energetically expensive immune responses. Individuals inhabiting high pathogen-risk environments may benefit from decreased testosterone levels to avoid immunosuppression and suspend energetically expensive anabolic functions (Muehlenbein 2008). Environmental conditions, including infection, during development may ultimately play an important role in altering baseline testosterone (and other hormone) levels as well as amount of variation experienced in adulthood. *The hypothesis that the benefits of testosterone trade off with immune function is based on the assumptions that immune functions are energetically costly, and that hormones play important roles in the regulation of immunity*. The immunomodulatory actions of these hormones are complex and varied, and altering the hormonal milieu may result in differential susceptibility to both infectious and chronic diseases.

7.2 Trade-Offs and Immunity

The immune system (see Box 7.1 and Fig. 7.1) is an excellent example of a reaction norm with both short- and long-term phenotypic plasticity in response to ecological stressors such as pathogens, allergens, and injury. Immunocompetence, or the ability to mount an effective immune response, is obviously an integral component of organismal life histories because it is crucial for maximizing evolutionary fitness. And because immunocompetence is an integral part of organismal life histories, it is predicted to be involved in physiological trade-offs with other functions (Sheldon and Verhulst 1996; Lockmiller and Deerenberg 2000; Norris and Evans 2000; Barnard and Behnke 2001). Selection for trade-offs is expected to be particularly strong under conditions of resource restriction, when development, maintenance, and activation of immune responses generate a substantial energetic burden (Sheldon and Verhulst 1996; Lockmiller and Deerenberg 2000; Schmid-Hempel 2003; Muehlenbein and Bribiescas 2005) (see Box 7.2).

Optimized immune functions should trade off with a variety of critical life history functions in humans, including growth and reproduction. In children, chronic immune activation in various conditions is associated with growth faltering, the failure to achieve normal growth potential (intestinal infections: Checkley et al. 1998; Campbell et al. 2003; Hadju et al. 1995; HIV infection: Arpadi 2000; inflammatory bowel disease: Ballinger et al. 2003). Likewise, nutrient deficiencies can have significant, long-term negative effects on the human immune system (Lunn 1991; Gershwin et al. 2000). Elevated C-reactive protein levels (a general measure of inflammation) are reported to be associated with reduced gains in height across 3 months in Tsimane children of Amazonian Bolivia (McDade et al. 2008). Boys in Nepal with high levels of acute-phase proteins (other proteins also associated with inflammatory states) have demon-

strated stunted growth (Panter-Brick et al. 2000). Similar associations between childhood immune activation and decreased growth have been found in British children (Panter-Brick et al. 2004).

Clearly the literature points to associations between growth reduction and increased immune activation, consistent with expectations of life history theory. Illness during development may also delay menarche, as was the case for a sample of Danish women infected with *Helicobacter pylori* (Rosenstock et al. 2000) and in Guatemalan women with intestinal infections (Khan et al. 1996). Earlier menopause might also result from chronic immune activation (Cramer et al. 1983; Dorman et al. 2001). *Trade-offs between immunity and reproduction can also be identified by observing correlated changes in hormonal mechanisms responsible for the manifold interactions between these two systems*. This is particularly the case for testosterone, estradiol, and dehydroepiandrosterone.

Box 7.1: Major Mechanisms of Human Immunity

Although a comprehensive review of the human immune system is beyond the scope of this discussion (see Paul 2008), here we offer a minute summary to orient the reader (Fig. 7.1). This is meant *only* to illustrate the complexity of the immune system's dynamic responses. Typically, the human immune system is organized into two primary components innate (constitutive, nonspecific) and adaptive (acquired, specific). Innate responses include rapid mechanisms to block and eliminate foreign particles from host invasion, such as anatomical barriers, basic health behaviors, resident bacteria, humoral factors (e.g., lysozyme), and cells like neutrophils, monocytes, macrophages, basophils, mast cells, eosinophils, and natural killer cells. These cells exhibit a number of functions, from phagocytosis and cytokine secretion to chemotaxis and antigen processing and presentation. Lactoferrin, transferrin, heat shock proteins, and other soluble factors possess a variety of antimicrobial functions. The complement system includes enzymes that function to eliminate microorganisms by promoting inflammatory responses, lysis of foreign cells, and mediation of phagocytosis.

Secondary immune responses during subsequent exposures are facilitated through acquired immune mechanisms that typically involve lymphocytes (both T and B cells). B cells, produced from stem cells in bone marrow, represent antibody-mediated (humoral) immunity that involves the secretion of antibodies or "immunoglobulins" (i.e., IgG, IgM, IgA, IgD, and IgE). Antibodies neutralize pathogens and their products, block binding of parasites to host cells, induce complement activation, promote cellular migration to sites of infection, and enhance phagocytosis, among other actions. T cells, which develop in the thymus, represent cellular immunity. Different subsets of T cells are identified by their surface markers (CD numbers) that regulate cellular activation and adhesion. Cytotoxic T cells (CD8) destroy infected host cells via perforin and lysis. Suppressor T cells downregulate T cell

(continued)

Box 7.1: (continued)

responses after infection. Helper T cells (CD4) secrete cytokines and activate B cells to secrete antibodies. Cytokines are glycoproteins that perform a variety of functions such as regulation of cell growth and development. Single cytokines can have multiple functions, multiple cytokines can have similar functions, some cytokines work together to facilitate single functions, and some cytokines have opposite functions to one another.

CD4 helper T cells are generally differentiated into major subsets depending on the type of cytokine produced. For example, Th-1 cytokines include, among others, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), and various interleukins (IL-1β, IL-2, IL-3, IL-12, etc.). These cytokines activate macrophages, neutrophils, and natural killer cells, mediate inflammatory responses and cellular immunity (T cells), promote cytotoxicity toward tumor cells, and enhance chemotaxis of leukocytes. Th-2, anti-inflammatory cytokines include many interleukins (IL-4, IL-5, IL-6, etc.) that induce humoral immunity and antibody production (B cells), eosinophil activation, mast cell degranulation, goblet cell hyperplasia, mucin production, and intestinal mastocytosis (resulting in histamine release). Despite the fact that Th-1 and Th-2 cytokines act antagonistically to one another, both are usually present within the host at any given time, although during infection one phenotype may predominate. Other Th cell types include Th-17, Tregs, Th-3 and possibly others. Clearly, single measures of immunity are not capable of capturing the complexity of such a response.

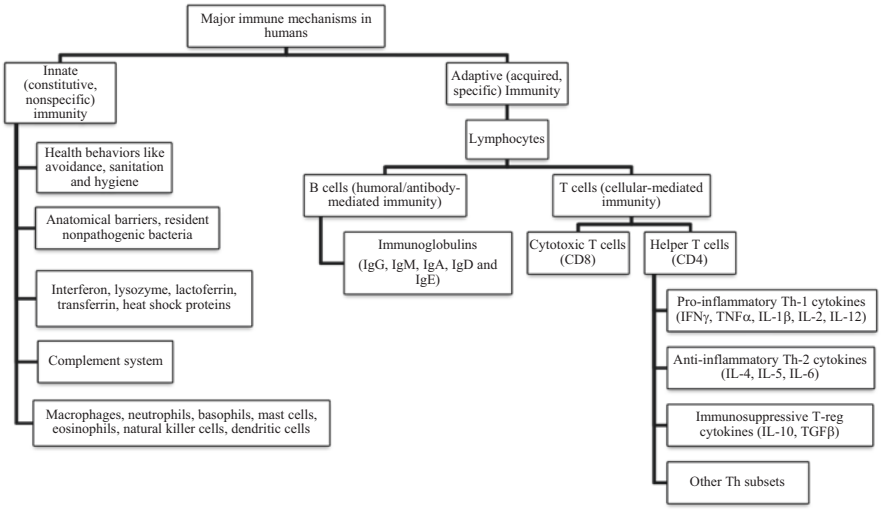

Fig. 7.1 Major immune mechanisms in humans. An illustrated summary of the complexity of the immune system's dynamic responses. For an explanation of the basic components (see Box 1). For a more comprehensive review of the human immune system (see Paul 2008). Modified from Muehlenbein (2010)

Box 7.2: Human immunity Is Energetically Expensive
In humans, prolonged energy and nutrient restriction as well as intense physical exercise can lead to immunosuppression (Chandra and Newberne 1977; Gershwin et al. 1984; Chandra 1992; Kumae et al. 1994; Pedersen and Toft 2000; Field et al. 2002); conversely, supplementation with calories, micro- and macronutrients can offset age-related declines in immunity (Wouters-Wesseling et al. 2005). The physical and psychological stress of physical exertion associated with elite athletic competitions or military training has been shown to be associated with increased incidence of upper respiratory tract infections (Peters and Bateman 1983; Nieman et al. 1990; Gomez-Merino et al. 2005). Acute infection in adult humans can cause abnormal protein loss—greater than 1 g per kilogram of body weight per day (Scrimshaw 1992). In humans, the rapid, constant turnover of T and B cells is very likely to be energetically demanding (Macallan et al. 2004, 2005).

Severe perturbations like sepsis, burns, trauma, and surgery are associated with a 25–55 % increase in resting metabolic rate compared with that in healthy subjects, as well as a reduction in body weight and total body protein (Arturson 1978; Long 1977; Kreymann et al. 1993; Frankenfield et al. 1994; Biolo et al. 1997; Carlson et al. 1997; Uehara et al. 1999; Genton and Pichard 2011), and an increase in nitrogen excretion (Carlson et al. 1997; Hasselgren and Fischer 1998). Fever typically results in a 7–15 % increase in resting metabolic rate for every 1 °C rise in body temperature (Barr et al. 1922; Roe and Kinney 1965; Elia 1992). Even in the absence of fever, resting metabolic rate is elevated during infection. For example, in a sample of 25 nonfebrile young men naturally infected with respiratory tract pathogens, resting metabolic rate was elevated by 14 % compared to samples taken after convalescence (Muehlenbein et al. 2010). Further research is needed to investigate changes in metabolic rates of adult humans during illnesses of varying severities and with different states of energy balance.

7.3 Testosterone and Immunity

Testosterone's immunomodulatory actions have usually been described as suppressive, although the results of a multitude of studies using a variety of host species are surprisingly mixed (see Muehlenbein and Bribiescas 2005 for review). In vitro experiments suggest that testosterone can increase suppressor T cell populations (Weinstein and Bercovich 1981), reduce resistance against oxidative damage (Alonso-Alvarez et al. 2007), reduce T-helper cell function (Grossman et al. 1991; Wunderlich et al. 2002), inhibit cytokine (Daynes and Araneo 1991; Grossman 1995) and antibody production (Olsen and Kovacs 1996), and impair natural killer cell and macrophage activity (Straub and Cutolo 2001). Testosterone may alter the

CD4+/CD8+ T-cell ratio in favor of CD8+ cells (Olsen et al. 1991; Weinstein and Bercovich 1981), and also favor the development of Th1 cytokines (Daynes et al. 1991; Giltay et al. 2000). *There is no reason, however, to believe a priori that testosterone should affect all aspects of immunity equally*.

Results of in vivo studies of the relationship of testosterone levels to immune status in humans are equivocal. A majority of studies conducted on healthy participants reveal few associations between testosterone and immunity. For example, in a large sample of healthy military men, Granger et al. (2000) found no association between serum testosterone levels and T or B lymphocytes, although testosterone and IgA levels were negatively correlated. No association between testosterone and IgA was identified in a smaller study of young adults (van Anders 2010). In a study of healthy male athletes, there were no associations found between testosterone and the cytokines IL-6 or IL-1β (FitzGerald et al. 2012). In a sample of 94 healthy young adults with very detailed exclusion criteria and a multi-sample collection regime, salivary testosterone levels were actually directly (positively) related to a functional measure of innate immunity (the capability of lysozyme, antibodies, complement and cells in saliva to lyse and inhibit growth of pathogenic bacteria; see Muehlenbein et al. 2011; Prall et al. 2011). Of course, variation in sampling regime, assays or laboratory conditions may explain some of the differences between studies. It is also critical to limit conclusions based on single measures of immunity, as this obviously may not accurately reflect functional immunity in terms of the ability to fight pathogens as a coordinated system (Sheldon and Verhulst 1996; Westneat and Birkhead 1998; Norris and Evans 2000). *Assays must be utilized that represent functional, integrated, biologically relevant measures of different immune pathways* (Boughton et al. 2011; Demas et al. 2011).

It is also likely that host condition and energy availability play central roles in the immunomodulatory actions of testosterone. In healthy individuals with high resource availability and relatively low energy expenditure, the immunological costs of maintaining high testosterone levels could be negated. During a disease state, in contrast, when immune functions are upregulated, those with higher testosterone (or those whom are less efficient at lowering their testosterone level; see below) may pay higher additional energetic costs and thus exhibit higher morbidity. For example, in a population of Honduran men naturally infected with *Plasmodium vivax*, those with higher testosterone during infection had significantly higher levels of malaria parasitemia (Muehlenbein et al. 2005). These men also had elevated cortisol levels during peak illness compared to recovery or to age-matched healthy controls. It seems very likely that the hormonal milieu, of which testosterone is only a small part, and including the stress endocrine axis, affects the course and outcome of infection. Glucocorticoids may play a larger role in immunoregulation than does testosterone (Turnbull and Rivier 1999).

The assumption that testosterone is globally immunosuppressive—a common, but unsupported idea in the literature—is obviously inappropriate. *Under certain conditions, testosterone's actions on immunity may in fact be beneficial*. Testosterone may actually help to prevent certain forms of immunopathology (Burger and Dayer 2002). For example, testosterone suppresses circulating immune complexes during

malarial infection, which may help prevent immunopathological effects of this disease (Coleman et al. 1982). Testosterone may prevent the production of excess cytokines that might otherwise lead to tissue damage during meningitis and rheumatoid arthritis (Beutler and Cerami 1988; Waage et al. 1989). Testosterone might also function to redistribute immune cells to different parts of the body during infection (Braude et al. 1999).

Another line of evidence that testosterone is involved in mediating trade-offs between reproduction and immunity lies in its demonstrated responsiveness to illness, injury, and immune activation. Testosterone levels typically decrease in response to illness, and often correspond to the severity of perturbation (Spratt et al. 1993). Muehlenbein et al. (2005) identified lowered testosterone levels in Honduran men naturally infected with *Plasmodium vivax* compared with age-matched healthy controls. Similarly, in a sample of 25 nonfebrile young men naturally infected with respiratory tract pathogens, testosterone levels were lowered by an average of 30 % compared to those measured after recovery (Muehlenbein et al. 2010).

Variation in testosterone, and possibly other hormones, during illness may act as a physiological mechanism to decrease energy investment in reproductive effort (Muehlenbein and Bribiescas 2005; Muehlenbein 2008). This would be expected to be particularly important in high disease-risk environments and during times of limited energetic resources. Not only would depressed testosterone levels during immune activation work to limit energetic investment in energetically expensive anabolic functions, but it would also function to prevent immunosuppression by the higher testosterone levels that would be present otherwise (Folstad and Karter 1992; Wedekind and Folstad 1994; Sheldon and Verhulst 1996; Muehlenbein 2008). *Measuring changes in other hormone levels, including estrogens and leptin, during illness and throughout convalescence would be informative.*

7.4 Dehydroepiandrosterone and Immunity

As with testosterone, there has been a substantial amount of research on the immunological effects of dehydroepiandrosterone (DHEA). DHEA is a regnantoid hormone produced in the zona reticularis of the adrenal glands. DHEA and its sulfated ester DHEAS are implicated in a number of important physiological and behavioral functions. They appear to inhibit several innate immune processes, including inflammatory (Young et al. 1999; Coutinho et al. 2007) and complement responses (McLachlan et al. 1996). While this might help to ameliorate some chronic disorders, it could also increase the likelihood of impaired defense against infections. However, this liability appears to be counterbalanced by a stimulatory effect on adaptive immunity, including the development of lymphocytes (Daynes et al. 1990), particularly helper T cell activity (Suzuki et al. 1991), and proliferation of peripheral blood mononuclear cells (Sakakura et al. 2006). It is possible that DHEA also facilitates the production of Th2 over Th1 cytokines (Powell and Sonnenfeld 2006). DHEA has also been implicated in increasing Treg cytokine production (Auci et al. 2007; Coles et al. 2005).

DHEA may enhance immune responses against influenza (Corsini et al. 2006), malaria (Kurtis et al. 2001), leishmaniasis (Galindo-Sevilla et al. 2007), intestinal helminthes (Coutinho et al. 2007), and HIV (Wisniewski et al. 1993). Given the diversity of immune responses responsible for controlling such infections, however, *it is likely inappropriate to generalize DHEA's immunostimulatory effects*. Its effects may depend, in part, on the relative concentration of other hormones present. For example, in a population of 25 young men with nonfebrile acute respiratory tract infection, the ratio of DHEA to testosterone was higher during illness than after complete recovery (Prall and Muehlenbein 2011). We argue that elevated DHEA relative to testosterone might facilitate immune processes, and that a reversal of the DHEA/testosterone ratio following convalescence would downregulate immunity to prevent autoimmune reactions and bias energy expenditure towards other functions, like reproduction. These endocrine responses presumably are adaptive shifts to modulate allocations toward more immediate needs.

7.5 Estrogen and Immunity

Estradiol and other estrogens appear to be immunostimulatory. Higher circulating estrogen levels in women compared to men may help explain why females typically exhibit higher CD4+ helper T cell Th-2 cytokine responses (Bijlsma et al. 1999), greater B cell function (Soucy et al. 2005), lowered rates of cellular apoptosis (Grimaldi et al. 2002), enhanced cellular proliferation (Cutolo et al. 2005), and greater antibody secretion (Straub 2007; Cutolo et al. 2012), all of which may translate into lower morbidity and mortality from infectious diseases (Whitacre 2001). 17-beta estradiol is associated with increased immunoglobulin and cytokine levels (Olsen and Kovacs 1996; Cutolo et al. 2006). Estrogens have been shown to upregulate the production of antioxidant enzymes (Vina et al. 2006) that may decrease oxidative damage to mitochondrial DNA (Borras et al. 2007) and protect against the oxygen radicals produced by inflammatory stress (Asaba et al. 2004). Moreover, estrogens exhibit immunoprotective and anti-inflammatory properties following trauma and severe blood loss (Angele et al. 2001; Knoferl et al. 2001) and they (in contrast to testosterone, which exacerbates) protect against neuronal damage during hypoxia associated with ischemic stroke in rats (Nishino et al. 1998).

Women are naturally exposed to varying levels of estrogens as a result of cyclical variation throughout the menstrual cycle, very high levels throughout pregnancy, and a relative absence following menopause. Such variation may have important life history outcomes (Abrams and Miller 2011). Elevated levels of estrogens during ovulation and pregnancy, for example, may promote implantation and maintenance of pregnancy through anti-inflammatory (Th2) effects and temporary suppression of cell-mediated immunity (Whitacre et al. 1999; Whitacre 2001) as well as innate responses (Wira et al. 2010). Elevated progesterone levels during pregnancy appear to inhibit cytokine production (Golightly et al 2011). Therefore, during times of particularly heavy investment in female reproduction, there appears to be less investment in immunity. This appears to change when estrogens fall prior to and

around menopause and there is an increase in cytokine responses (Pfeilschifter et al. 2002). But in the absence of estrogens in postmenopausal women, immune functions can become significantly impaired (Giglio et al. 1994).

Elevated levels of estrogens may contribute to the higher prevalence of autoimmune diseases seen in women (Tanriverdi et al. 2003; Straub 2007; Cutolo and Straub 2009). These disorders represent a leading cause of death and serious disability in young and middle-aged women in the USA (Cantorna and Mahon 2004), and the incidence in women compared to men is increasing significantly (Chighizola and Meroni 2012). Oral contraceptive users are at higher risk of inflammatory bowel diseases (Khalili et al. 2012) and systemic lupus erythematosus (Bernier et al. 2009). *The effects of hormone replacement therapy on health measures predicted by life history trade-offs are of critical consideration today*.

7.6 Costs and Benefits of Hormone Therapy and Supplementation

Hormone supplementation is used clinically to treat a variety of conditions. One of the most well-studied examples is estrogen therapy in women, which is often used to treat menopausal symptoms. Estrogen therapy during the menopausal transition has been shown to substantially reduce the risk of osteoporosis. It is prescribed primarily for menopausal symptoms including hot flashes (or "flushes"), insomnia, and irritability; it may also improve mood, cognitive status, and memory (NAMS 2012; Wharton et al. 2011) (see Chap. 9 in this volume). However, hormone therapy (estrogen, or estrogen in combination with progesterone) in older women has been implicated in some large clinical trials with an increased risk of blood clots, stroke, and breast cancer (Stuenkel et al. 2012). The role that estrogen plays in the risk of cardiovascular disease in older women remains controversial; this hormone, like testosterone, clearly is associated with complex physiological trade-offs that are still poorly understood.

Androgenic anabolic steroids are often used to increase quality of life and strength in both men and women (Emmelot-Vonk et al. 2008; Bhasin et al. 2010). Testosterone has been used to increase libido and improve mood (Monga et al. 2002; Gray et al 2005; Knapp et al. 2008; Panay et al. 2010), although results can be mixed (Kenny et al. 2004). Testosterone has also been used to improve memory and some measures of depression (Cherrier et al. 2001; Pope et al. 2003). Intramuscular injections of testosterone enanthate following severe burn injury can ameliorate protein catabolism, amino acid efflux, and loss of lean body mass (Ferrando et al. 2001). Similar results have been found using Oxandrolone, a synthetic derivative of testosterone, in pediatric burn patients (Tuvdendorj et al. 2011), and administration to a large sample of adult burn patients resulted in a significant reduction in mortality (Pham et al. 2008). Androgenic anabolic steroids can also ameliorate cachexia associated with cancer, renal and hepatic failure, chronic obstructive pulmonary disorder, muscular dystrophy, trauma following major

surgery and anemia associated with leukemia or kidney failure (Mendenhall et al. 1995; Ferreira et al 1998; Basaria et al. 2001; Orr and Fiatarone 2004).

It is estimated that 6.5 million men in the USA will develop symptomatic, clinically recognized androgen deficiency (including lowered mood, energy and libido) by 2025 (Araujo et al. 2007). Most men with androgen deficiency either do not seek treatment for it, or are asymptomatic (Hall et al. 2008). Regardless of the cutoff values used to diagnose low testosterone, the availability of treatments and advertising by drug companies have increased. *The long-term effects of testosterone supplementation on specific aspects of health, including immune function, are largely unknown*. This problem is compounded by an increasing incidence of the use of anabolic androgenic steroids and other ergogenic (performance-enhancing) drugs for athletic enhancement or improvement of appearance (Cohen et al. 2007). The problem is not limited to professional athletes; particularly, worrisome is the dramatic rise in illegal steroid use in high school students (Calfee and Fadale 2006).

Steroid abuse in otherwise healthy individuals clearly can cause significant physical and psychological damage. These effects include a variety of conditions, from altered testicular function (Torres-Calleja et al. 2001) and acne (Walker and Adams 2009) to liver failure (Ishak 1981) and heart failure (Achar et al. 2010). Psychological effects (e.g., depression, psychosis, violence, aggression, impulsiveness, etc.) can be quite severe (Pope and Katz 1994; Bahrke et al. 1996; Beaver et al. 2008). The legal (clinical) and illegal (recreational) use of anabolic steroids has also been linked to an increased risk of prostate cancer (Shaneyfelt et al. 2000; Gaylis et al. 2005), although some studies have identified no such links (Roddam et al. 2008; Drewa and Chlosta 2010). However, the responsiveness of prostate cancer to treatments using androgen receptor inhibitors, GnRH agonists and antagonists, and even surgical castration do support an association between testosterone and prostate cancer severity and progression (Denmeade and Isaacs 2002).

The effects of testosterone supplementation on human immunity are not well investigated. In the entire volume on testosterone supplementation by Nieschlag et al. (2012), immunological consequences are mentioned only sporadically and briefly, and results of studies cited have yielded mixed results. Varying doses of testosterone do not appear to affect lymphocyte counts or viral load in HIV-infected men (Bhasin et al. 2000) and women (Choi et al. 2005; Looby et al. 2009). Testosterone treatment decreased CD4+ cell count in one study of postmenopausal women (Zofkova et al. 1995). In another study of otherwise healthy young men, there were no effects of testosterone enanthate on C-reactive protein levels (Singh et al. 2002), whereas Klinefelter's (XXY) syndrome patients have been shown to exhibit decreases in antibody levels and T cell counts following treatment with testosterone, although the percentage of CD8+ cells increased (Kocar et al. 2000). Similarly mixed results were identified by Muehlenbein and Bhasin (2012): of 52 healthy men ages 60–75 years, those who received monthly intramuscular injections of 600 mg of testosterone enanthate for 5 months showed increases in monocyte and neutrophil percentages but lowered eosinophil and lymphocyte percentages. As stated before, testosterone clearly does not affect all aspects of immunity equally, even as a result of clinically controlled supplementation.

There has also been an increased usage of DHEA by the American public as a dietary supplement in recent years (Baulieu et al. 2000). DHEA may influence metabolism and body composition, particularly through its conversion to testosterone and estradiol (Villareal and Holloszy 2004). Although other studies have identified no such relationships between body condition and DHEA level (Callies et al 2001; Percheron et al. 2003), its use as an anti-obesity agent continues to grow (Ip et al. 2011). DHEA is also purported to ameliorate some measures of depression (Wolkowitz et al. 1999) and to increase libido (Arlt et al. 1999). However, given its role as a prohormone, there are likely many other risks to supplement use, including breast cancer (Gordon et al. 1990) and ovarian cancer (Helzlsouer et al. 1995); the magnitude of risk associated with this supplement remains unknown.

Like testosterone, DHEA supplementation does not appear to affect lymphocyte counts or viral load in HIV-infected individuals (Rabkin et al. 2006; Abrams et al. 2007). Some studies have shown that DHEA supplementation may increase immune response to vaccine (Araneo et al. 1995), whereas other studies have found no such effects (Danenberg et al. 1997). DHEA may increase NK cell activity and other cellular responses in elderly recipients (Khorram et al. 1997; Casson et al. 1993), although other studies have revealed no change in these measures (Kohut et al. 2003).

The effects of hormone supplementation on the immune system require much more research to determine if the benefits of hormone therapy truly outweigh the costs. A simple prediction based on life history theory is that alterations in the hormonal mechanisms responsible for facilitating trade-offs between immune and other functions will result in dysregulation of this balanced system. Future analyses must include detailed effects of androgens and estrogens in men and women, utilizing various functional measures of adaptive immunity in a variety of experimental regimes: during health and illness of varying severity, and in people experiencing varying degrees of energy flux. *Trade-offs between immunity and other functions may only become apparent under certain conditions, or during particular critical windows at certain points in the life course*.

7.7 Summary

Phenotypic plasticity in response to stochastic ecological stressors like pathogens represents a suite of complex adaptations, and our immune system epitomizes a reaction norm that allows for adaptation to pathogens, allergens, and injury. Because immune responses presumably generate a substantial energetic burden, optimization of immunity during illness should result in decreased energetic investment in other functions, including growth and reproduction. It should be possible to indirectly observe such trade-offs by measuring correlated changes in hormones, since endocrine mechanisms are sensitive to environmental cues that can otherwise facilitate modulation of immunity relative to reproductive effort and other investments.

Testosterone, DHEA, and estradiol all appear to have complex immunomodulatory actions. Whereas testosterone's actions have usually been hypothesized to be suppressive, results of studies addressing this premise are surprisingly mixed. The same can be said for the possible immunostimulatory actions of DHEA. Estradiol may also play

an important role in moderating risks of both infectious and autoimmune diseases. In short, the fluctuating, complex hormonal milieu may affect the course and outcome of disease directly through actions on immune effector mechanisms, as well as indirectly through adaptive shifts in life history allocation decisions. Although hormone supplementation clearly has beneficial actions under certain conditions, its effects on human immunity are not well investigated. Long-term augmentation of these hormonal mediators of life history trade-offs may impose significant costs on immunity against both infectious and chronic diseases.

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