Does Chronic Illness Cause Testosterone Deficiency?

James E. Griffin, MD

Department of Internal Medicine

Grand Rounds

The University of Texas Southwestern Medical Center

May 13, 2004

This is to acknowledge that Dr. Griffin has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Griffin will be discussing off-label uses in his presentation.

James E. Griffin, MD
Diana and Richard C. Strauss Professor of Biomedical Research
Associate Dean for Academic Planning
Division: Endocrinology
Rank: Professor
Interests: Male reproductive physiology, androgen action, clinical endocrinology

There has been a great deal of interest in the observation that testosterone levels in many healthy men decline significantly with age, the so-called andropause. The possibility that many older men might be candidates for testosterone therapy has stimulated the development of new delivery systems for testosterone therapy such as the testosterone patch and testosterone gel. Many of these men with the low testosterone of aging have mild symptoms suggestive of testosterone deficiency while most do not have symptoms. In all of the older men with low testosterone there are subtle alterations in hypothalamic-pituitary function and impaired response of the testes to gonadotropin stimulation. Although most endocrinologists are comfortable treating older men with clear symptoms of testosterone deficiency and unequivocally low bioavailable testosterone levels, many feel that large controlled studies of the risk/benefit ratio are needed because of concerns about adverse effects in regard to the prostate. The unexpected findings of the Women's Health Initiative in regard to the adverse effects of HRT in women have made physicians uncomfortable about making plans to prescribe hormone replacement to such a large number (possibly half) of aging men.

Today I would like to focus on another group of men with testosterone deficiency. These are men with chronic illnesses in whom the side effects of the illness lead to variable decreases in testosterone levels. In some instances the testosterone deficiency may contribute to the overall morbidity and impact further on the disease mechanisms.

Defining Testosterone Deficiency

The Hypothalamic-Pituitary-Testicular Axis

The hypothalamus communicates with the pituitary gland both by a portal vascular system and by neural pathways. The portal vascular system provides a mechanism for the delivery of releasing hormones from the brain to the pituitary gland, the major system by which the brain controls anterior pituitary function. The preoptic area and the medial basal region of the hypothalamus (particularly the arcuate nucleus) contain important centers for control of gonadotropin secretion. Peptidergic neurons in the arcuate nucleus secrete gonadotropin-releasing hormone (GnRH) in small bursts about every two hours in men. GnRH travels through the portal system and stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gonadotropes. LH acts in the Leydig cells of the testis to stimulate testosterone secretion, and FSH, in concert with intratesticular testosterone, acts in the seminiferous tubules in the Sertoli cells to stimulate sperm production and the secretion of the peptide hormone inhibin. Pulses of LH reflect the pulsatile pattern of GnRH secretion. Several hormones and neurotransmitters modulate GnRH and gonadotropin secretion (Figure 1).

Testosterone exerts a negative feedback on GnRH and gonadotropin secretion, whereas inhibin has a negative feedback specifically on FSH secretion (1). The negative feedback of androgens and estrogens on LH is mediated by an opioid pathway (2). The negative feedback of testosterone on FSH secretion appears to be mediated by its conversion to estradiol (3). Prolactin, corticotrophin-releasing hormone (CRH), and cytokines all have inhibitory effects on GnRH secretion. Leptin, a peptide hormone secreted by adipocytes,

has been demonstrated to enhance GnRH secretion (4). A rise in free or bioavailable leptin occurs just before the onset of puberty (5). Gonadal steroidogenesis is also modulataed by cytokines secreted by gonadal macrophages (6).

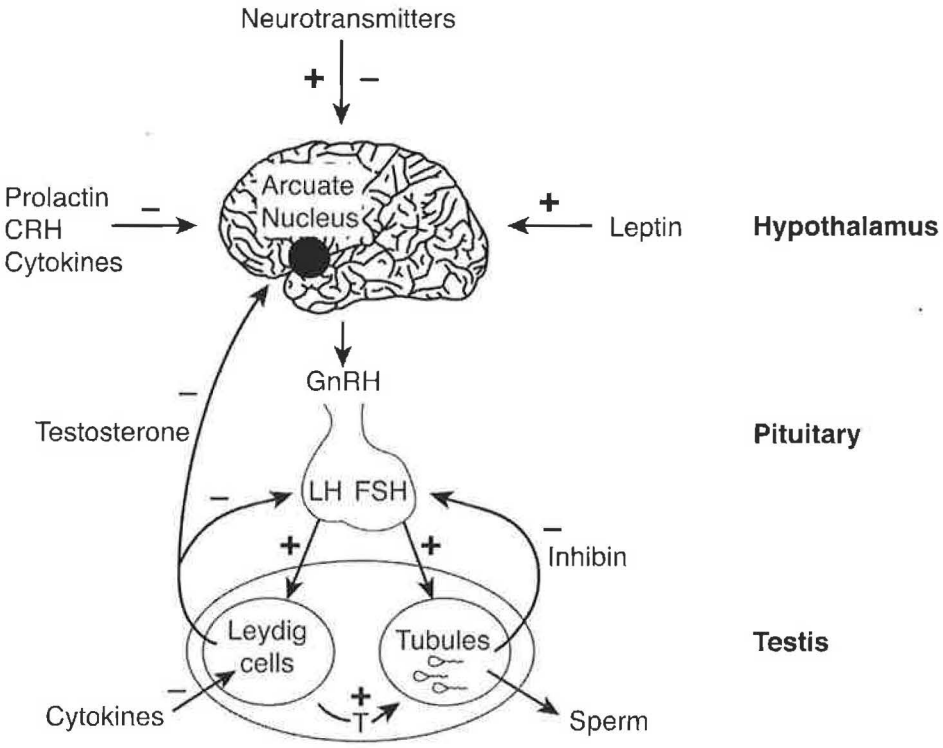

Figure 1. The Hypothalamic-Pituitary-Testicular Axis.

Effects of Testosterone

Testosterone exerts effects in a variety of target organs (Figure 2) including the brain, muscle, kidney, bone marrow, bone, male sexual organs, adipose tissue, liver, and skin (1). In the brain testosterone stimulates libido; in muscle it increases the mass and strength; in the kidney it stimulates erythropoietin production; in bone marrow it stimulates stem cells; in bone it accelerates linear growth and increases bone mineral density; in adipose tissue it decreases subcutaneous and deep stores; in the male genital tract it stimulates penile growth, spermatogenesis, and prostate growth and function; in liver it affects synthesis of serum proteins; and in skin it mediates hair growth, balding, and sebum. Although the anabolic effects of testosterone to stimulate growth of muscle are often listed separately from its androgenic (or virilizing) effects, it has not been possible to synthesize anabolic steroids that do not have androgenic effects (1).

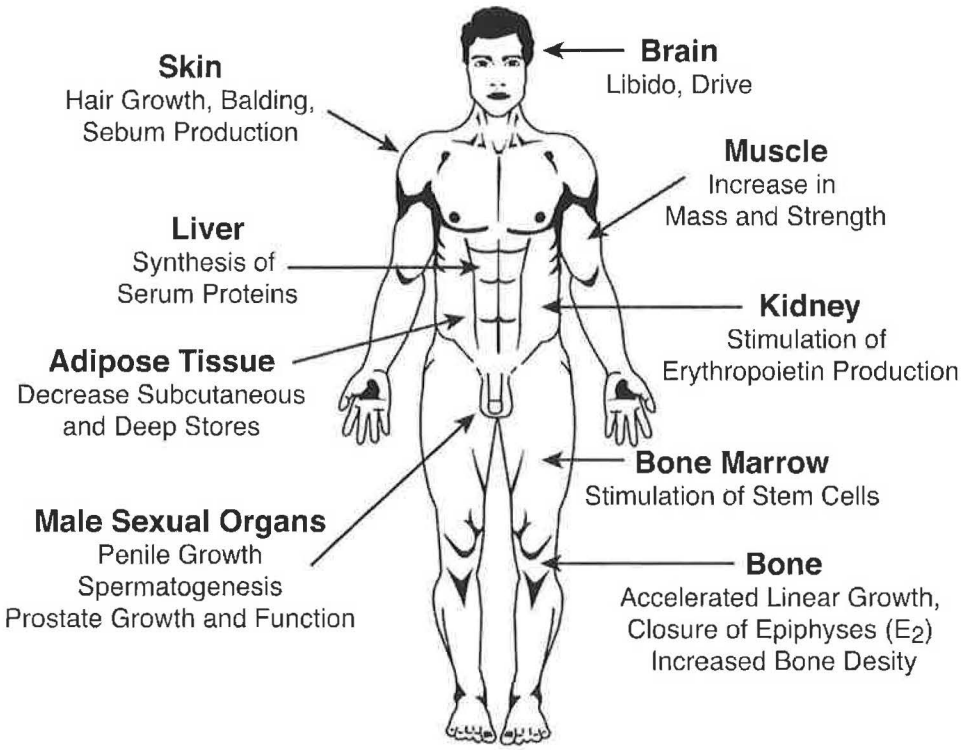

Figure 2. Testosterone Target Organs

Testosterone exerts some of its effects via conversion to its active metabolites, dihydrotestosterone (and other 5α-reduced androgens) and estradiol. Dihydrotestosterone, formed at its site of action in target tissues, mediates formation of the prostate and external genitalia during embryogenesis and most of the changes associated with male sexual maturation at puberty except growth of skeletal muscle which is thought to be mediated by testosterone itself. Testosterone itself is also thought to regulate gonadotropin secretion and spermatogenesis. Although testosterone stimulates linear growth of bone, estradiol formation is required for fusion of the epiphyses at completion of male puberty.

Assessing Adequacy of Serum Testosterone Concentrations

Testosterone circulates largely bound to serum proteins with only about 2% of the total testosterone in normal men unbound in *in vitro* tests of peripheral blood. About 44% is tightly bound to sex hormone-binding globulin (SHBG), and 54% is weakly bound to albumin and other serum proteins (1). Albumin has about 1000-fold lower affinity for testosterone than does SHBG, but albumin has an approximately 1000-fold greater binding capacity than does SHBG so that the binding capacity is similar. The proportion of testosterone bound to SHBG in serum is directly related to the concentration of SHBG.

Protein-bound testosterone can dissociate within the capillary bed so that the active fraction is actually larger than the free fraction as estimated by equilibrium dialysis (7). In fact, nearly all the albumin-bound testosterone is available for tissue uptake *in vivo* so that the bioavailable testosterone in normal lean men is about half of the total (equal to the free plus the albumin-bound fractions). This bioavailable testosterone is sometimes referred to as the non SHBG-bound testosterone and can be measured by assays of testosterone in serum following precipitation of the SHBG by ammonium sulfate. Accurate measurement of free testosterone requires the more cumbersome method of equilibrium dialysis. Kits used in many commercial labs to estimate free testosterone by analog methods are often inaccurate (8). An alternative method to accurately determine the concentration of both the free and the bioavailable testosterone is to measure the total testosterone, the albumin, and the SHBG concentration and calculate the free and bioavailable testosterone from the known binding constants for these carrier proteins (8). This method is available from Quest laboratories.

For total testosterone measurements, newer nonradioactive immunoassay kits and automated platform immunoassays that use chemiluminescent detection with testosterone analogs as standards have largely replaced the older radioimmunoassays (RIAs) that used pure testosterone standards with extraction and chromatography with rigorous validation of accuracy. These newer automated immunoassays use proprietary reagents and instrumentation with little published validation of their accuracy. Whereas the standard RIAs consistently had a normal range of 300-1000 ng/dl (10.4-34.7 nmol/liter), many of these newer assays have a lower normal range with the lower limit in the lower 200s or sometimes less than 200ng/dl. Matsumoto and Bremner think that a major contribution to this variation and decline in normal ranges has been a lack of attention to validation of accuracy for many of these assays (9). The relatively consistent underestimation of total testosterone levels by automated assays compared to liquid chromatography tandem mass spectrometry in the 100-300 ng/dl range is likely to provide problems in distinguishing eugonadal from mildly hypogonadal men (9, 10).

Total testosterone levels are decreased in conditions associated with reduced SHBG levels (e.g., moderate obesity, hypothyroidism, androgen, glucocorticoid or progestin use, nephrotic syndrome) and increased in situations associated with elevated SHBG levels (e.g. aging, hyperthyroidism, androgen deficiency, estrogen or anticonvulsant use, hepatic cirrhosis) (1). If clinical conditions associated with alterations in SHBG exist, measurement of free or bioavailable testosterone should be used to assess possible testosterone deficiency.

Just as LH is secreted in a pulsatile manner, testosterone concentrations in serum have a pulsatile pattern when monitored at frequent intervals (1). In addition, serum testosterone concentrations in normal young men have a diurnal variation with morning levels higher than late afternoon values. The late afternoon values may be as much as 30% lower than the 8-10 a.m. values (11). This diurnal pattern does not occur in older men (11). Thus, to avoid misinterpretation of testosterone values it is preferable to obtain serum testosterone measurements in the morning, and borderline values should be reassessed by measuring three pooled samples at 20 minute intervals to avoid sampling errors (1).

Acute Illness Causes Testosterone Deficiency

Acute Critical Illness and the Hypothalamic-Pituitary Testicular Axis

A number of studies have demonstrated that the hypothalamic-pituitary-testicular axis (H-P-T axis) is dramatically altered during acute critical illness or following major surgery (12-20). These effects are not disease specific but have been observed in sepsis, burns, myocardial infarction, acute respiratory syndromes, leukemia, and surgery. The serum level of testosterone often decreases to a prepubertal level (Figure 3) (20). In most patients gonadotropin secretion is suppressed and recovers with resolution of the illness. In a subset of critically ill men (30% in one study), gonadotropin levels above the normal range have been observed accompanying a low serum testosterone concentration (14, 21). Neither the biopotency of the gonadotropins nor the binding of testosterone to SHBG changed across the course of the acute illness (21).

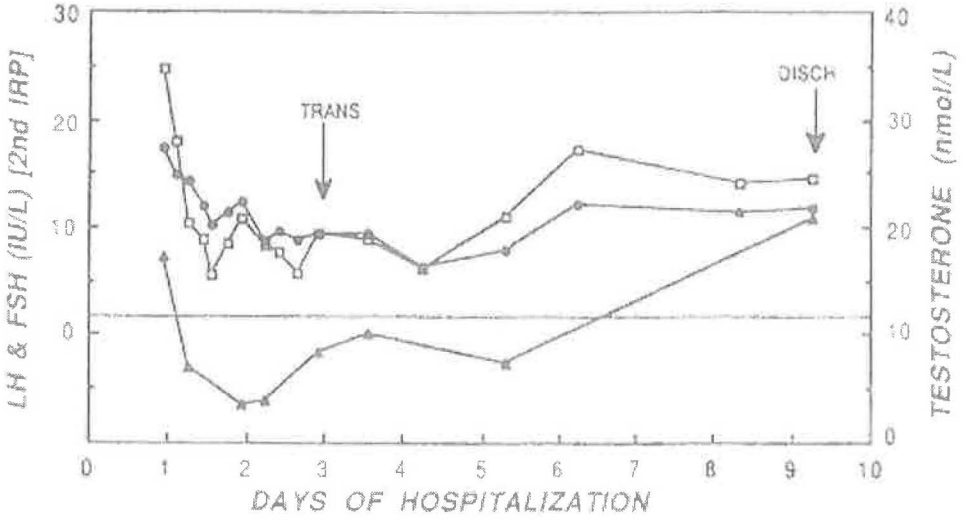

Figure 3. Serum levels of testosterone (triangles), LH (squares), and FSH (circles) throughout the hospitalization of a 43-year-old man with acute myocardial infarction. The solid line is the lower limit of normal testosterone in healthy men. TRANS = transfer to the floor; DISCH = discharge from the hospital (from ref. 20).

The degree of these changes in the H-P-T axis is related to the severity of illness (20). This has been illustrated in a study of 59 men hospitalized for an acute illness. To avoid confounding factors known to affect the H-P-T axis in the absence of critical illness, patients with head trauma, renal or hepatic failure, surgery, and alcohol abuse were excluded. Most men had MI or acute respiratory illness. Severity of illness was rated by the Acute Physiologic and Chronic Health Evaluation II scoring system (APACHE II) on admission. Although several drugs administered in critical care units are known to affect the H-P-T axis, analysis of drug effects in this large group could not account for either H-P-T axis suppression or its relation to severity of illness (20). Specifically, patients

receiving opiates, glucocorticoids, or dopaminergic agents did not have significantly lower levels of either gonadotropins or testosterone than patients not receiving these drugs. Admission cortisol values were not correlated with LH, FSH, or testosterone on admission or at day 3 of hospitalization. Similarly, day 3 cortisol values were not correlated with day 3 LH, FSH, or testosterone. The 60% of men with low testosterone on day 3 did not have a significantly different mean serum cortisol than men with normal serum testosterone. Neither serum prolactin on admission nor on day 3 was correlated with APACHE scores or serum concentrations of LH, FSH, or testosterone on admission or day 3. Men with low serum testosterone on day 3 did not have a higher mean serum prolactin level than men with normal serum testosterone. Overall, men with relatively mild or moderate illness had the same degree of suppression of testosterone, whereas hypogonadism was more pronounced in men with severe illness (Figure 4) (20).

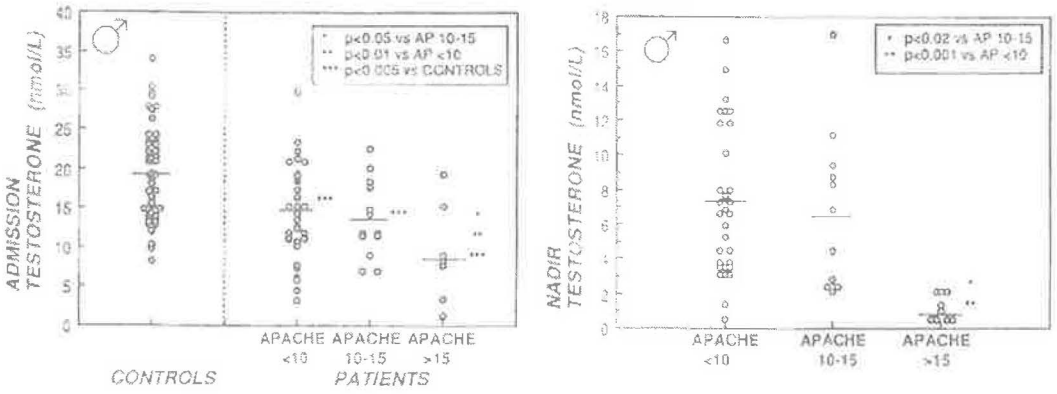

Figure 4. Serum testosterone levels in men grouped by disease severity at admission compared to healthy controls and serum testosterone at nadir during hospitalization (from ref. 20).

These observations suggest two thresholds for H-P-T axis suppression in acute illness: the first a relatively low level of illness, and the second threshold a more complete suppression with severe disease. The percentage of men with low bioavailable testosterone during prolonged critical illness (median ICU length of stay 25 days) in one study was 96% (29 of 30 men) (22).

Attempts to dissect the level of the defect in the H-P-T axis in prolonged critical illness have included pulsatile administration of GnRH to 15 critically ill men with prolonged ICU stay (25 ± 9 days) (23). With prolonged critical illness all men developed inappropriately low gonadotropins for the profoundly low testosterone levels. Five day pulsatile infusions of GnRH resulted in only transient increases in pulsatile LH secretion that were no longer evident by day 5. There was only a minimal rise in testosterone in spite of the significant initial increase in LH. These observations suggest a combined hypothalamic-pituitary-testicular defect.

Mechanisms for Suppression of the H-P-T Axis in Critical Illness

Several factors may play a role in the suppression of GnRH. The two major influences based on studies in animal models and humans are thought to be increased CRH secretion and increased production of cytokines. In animal models, CRH can rapidly and profoundly suppress GnRH secretion (24). CRH has this effect even when increases in serum cortisol are prevented by simultaneous administration of metyrapone. The frequency and duration of GnRH pulse activity are both affected. The prior administration of naloxone blocked the effect of CRH on pulse generator frequency. Some studies of CRH infusion in humans support this mechanism and suggest the enhanced endogenous CRH resulting from the stress of illness may be the mechanism for decreased gonadotropins (25, 26). As in the study in primates described above, in one human study the effect of CRH was blocked by administration of naloxone; and the reversal of the CRH effect by naloxone occurred even though cortisol levels were similarly elevated (25).

Studies in rats indicate that cytokines can also suppress GnRH and LH secretion (27). Cytokines are known to be present in areas of the hypothalamus close to the arcuate nucleus and undoubtedly have central effects on GnRH in humans as shown in animals. In addition, there is a systemic cytokine response to critical illness (28, 29). The serum concentrations of interleukins, tumor necrosis factor-α and interferons increase during major illness. The infusion of interleukin 6 (IL-6) and interferon-α (IFN-α) in men causes a marked fall in serum testosterone concentrations without change in LH (30, 31). Similar responses have been seen with tumor necrosis factor-α (TNF-α) in rats. IL-1, IL-6, TNF-α, and IFN-γ all inhibit Leydig cell steroidogenesis in culture (32-34). In addition, IFN-γ and TNF-α blunt the Leydig cell response to hCG and cyclic AMP in culture (33-35).

The cytokine suppression of Leydig cell steroidogenesis is caused at least in part by suppression of StAR gene expression (36, 37). Centrally released cytokines may have an effect on testicular steroidogenesis without increased peripheral cytokine levels. Intracerebroventricular (icv) injection of IL-1β resulted in decreased hCG-stimulated testosterone in the rat (38). The authors suspected stimulation of inhibitory pathways connecting the hypothalamus to the testes. Central β-blocker administration prevented the decrease in testicular responsiveness, and central administration of a β-adrenergic agonist mimicked the IL-1β administration on hCG responsiveness (38). A subsequent study confirmed the effect of icv IL-1β on testes studied *ex vivo* and found decreased levels of StAR (39). Thus it appears that central IL-1β administration activates a neural catecholamine-dependent pathway that connects the brain and the testes independently of the pituitary.

Is The Decrease in Testosterone Harmful to Critically Ill Patients?

In the face of life-threatening acute illness one might argue that it is better for the body to devote resources to the function of organs needed to survive rather than to the reproductive tract. However, in prolonged critical illness there is a catabolic state due to

the combined effect of glucocorticoid and catecholamine excess and decreases in anabolic hormones including testosterone and IGF I. The decrease in testosterone during critical illness would be predicted to have potentially adverse effects on lean body mass. Decreased skeletal muscle function could theoretically impair mobility and respiratory function. Decreased mobility could result in complications. However, these potential effects of a catabolic state have not been proved or disproved. Giving anabolic steroids to critically ill patients has been tried but has only been found to be beneficial in regard to patients with major burns in regard to the rate of weight gain and time for wound healing (reviewed in 40). However, in a general group of trauma patients no effect of anabolic steroid treatment could be detected in regard to nitrogen balance, length of stay in the ICU or hospital, or body cell mass (41). In several studies, mostly of burn patients, no adverse clinical effects were seen (40). In none of these studies was there an attempt to give testosterone selectively to those patients identified as have testosterone deficiency.

Chronic Illness and Its Treatment May Also Cause Testosterone Deficiency

Knowing the mechanisms for suppression of the H-P-T axis that exist in acute critical illness, the effects of chronic illness can now be evaluated in regard to the existence of cytokine excess or other mechanisms and identified abnormalities in gonadotropins and testosterone. Only selected non-endocrine disorders will be discussed.

Malnutrition

The classic study of severe protein-calorie malnutrition in 28 Indian men from Calcutta documented the changes in the pituitary-gonadal axis (42). All men had clinical manifestation of testosterone deficiency, and evidence for either pituitary or Leydig cell abnormalities or combined defects was found in 20 men. In these men who were selected for not having other illnesses, refeeding resulted in the disappearance of the hypogonadism along with the other manifestations of malnutrition (42).

The severe weight loss in men with disseminated cancer can result in a similar picture of abnormal gonadotropins and testosterone even prior to chemotherapy (43). In this group of 44 men, 88% were less than 90% of ideal body weight. Of the 44 men, 32 had a hormonal profile indicating a defect in the H-P-T axis. Significantly decreased ideal body weight was found in the group with low testosterone and low or normal LH.

An experimental model for the hypogonadism of weight loss has been explored by using short term fasting of healthy men. Studies suggest that acute effects of fasting affect the pulsatile secretion of LH and testosterone implying effects on the hypothalamic pulse generator releasing GnRH. To demonstrate that the primary abnormality was GnRH release, Aloi and colleagues studied six healthy men in an 83 hour fast with either pulsatile GnRH or saline every 90 minutes. GnRH infusion prevented the decrease in LH pulse frequency and amplitude and the 30% decrease in serum testosterone levels seen in the saline infusion group during this fast (44). Finally, studies of changes in leptin levels with fasting in animals had suggested a role for leptin in the decrease in GnRH pulsatility

and testosterone concentrations. Thus Chan and colleagues studied eight healthy lean men under four separate conditions: a baseline fed state and three 72-hour fasting studies with administration of placebo, low dose leptin, or replacement dose recombinant human leptin (45). Fasting resulted in a dramatic 90% decrease in serum leptin even though weight loss was only approximately 2 kg. Replacement dose leptin administration prevented the 35% decrease in serum total testosterone and the 31% decrease in mean serum LH. LH pulsatility was also restored. SHBG levels increased somewhat during the fast so that free or bioavailable testosterone likely decreased more than total. Values during the last day of the fast are shown in Table 1. Although day 3 serum leptin levels in the replacement leptin group were slightly higher than those in the fed state, they were still within the physiologic range for lean men.

Table 1. Serum leptin, total testosterone, SHBG, and LH on the third day of each fed or fasting state.

	Control Period	3 d Fast + Placebo	3 d Fast + rLeptin
Leptin (ng/ml)	3.20 ± 1.16	0.34 ± 0.13*	8.22 ± 3.93*
Testosterone (ng/dl)	528 ± 103	393 ± 111*	544 ± 104
SHBG (nmol/l)	25.7 ± 1.72	31.0 ± 3.40	28.0 ± 3.03
LH (mIU/ml)	3.40 ± 0.35	2.35 ± 0.30	3.85 ± 0.32

Values are mean ± SE; * $P<0.01$

The authors interpreted these studies as indicating that the fall in leptin with fasting may be both necessary and sufficient for the physiologic adaptation of the H-P-T axis which requires leptin levels above a certain threshold for activation.

Obesity

As mentioned above in the discussion of assessment of testosterone concentrations, obesity is associated with decreased levels of SHBG. The reports of free and bioavailable testosterone levels in obesity have been inconsistent in finding abnormalities. When studied in relation to the degree of obesity as assessed by body mass index (BMI), total, bioavailable, and free testosterone were all highly correlated inversely with the BMI (46). Vermeulen's group made a key observation in a study of obese men (BMI > 30) by separating them into moderate obesity (BMI < 35) and severe obesity (BMI >40) (47, 48). Whereas the total testosterone levels were decreased in both groups of obese men, the free testosterone was significantly lower ($P < 0.01$) only in the severe obesity group. Thus it is recommended to measure either free or bioavailable testosterone in assessing obese men for possible testosterone deficiency. If morbidly obese men have testosterone deficiency, what is the mechanism or mechanisms? These same investigators studied LH pulsatile secretion by frequent sampling and found decreased LH levels and LH pulse amplitude only in the severe obesity group (47, 48). The authors concluded that the defect in obesity must be primarily at the hypothalamic-pituitary level because prior reports of the testosterone response to hCG stimulation in obese men had been normal. The

abnormalities of gonadotropin secretion may be related to the known increased estrogen production in severe obesity (49). Adipose tissue is a major site of the aromatase enzyme that converts androgens to estrogens.

More recently, the role of leptin excess as a cause of low testosterone in obese men has been explored. Animal studies have shown that functional leptin receptors are present in rodent testis and cultured Leydig cells (50, 51). Concentrations of leptin similar to those found in severely obese men were shown to inhibit hCG-stimulated testosterone production (51). Moreover, cyclic-AMP stimulated testosterone production was also inhibited, and studies of steroid intermediates suggested a block distal to the production of progesterone. Studies of leptin in obese men and correlations of leptin levels to testosterone levels showed that leptin was the best hormonal predictor of lower free testosterone levels (52). Only severely obese men had a decreased testosterone area under the curve following hCG, and the ratio of 17-hydroxyprogesterone to testosterone was increased by hCG.

Yet another mechanism for obesity suppressing the H-P-T axis is the hypoxemia of the Pickwickian syndrome in which the hypoxia may be the cause of low testosterone because similar changes are seen in chronic obstructive lung disease (see section on Chronic Lung Disease below). In a case report of a 58 year old man with no previous illness who gained 20 kg after stopping smoking, daytime somnolence and inability to concentrate developed along with symptoms of testosterone deficiency (53). His serum testosterone was 142 ng/dl, and hypoxia with hypoventilation was found on further testing. There was no history to suggest chronic bronchitis or emphysema. After losing 20 kg of weight in two months, his testosterone was 638 ng/dl, and his hypoxia and hypoventilation were markedly improved.

HIV/AIDS as a Paradigm for Chronic Illness and Benefit of Testosterone Replacement

In the early studies of men with overt AIDS and wasting, 30% were found to have a decreased total testosterone (54). Recognition that almost all HIV patients have increased SHBG levels suggested the need to measure free or bioavailable testosterone in order to accurately assess possible testosterone deficiency. In men with wasting, free testosterone levels correlate with lean body mass (55). One might conclude from this that AIDS wasting is similar to starvation and that the testosterone deficiency is secondary to the weight loss. However, Dobs and colleagues performed a nested case-control study of HIV patients to assess whether the testosterone deficiency might precede the wasting defining weight loss (56). They had prior serum samples on the men who eventually developed wasting and matched a control group of HIV positive men who had not developed wasting. They excluded men from the case and control groups who had known endocrine abnormalities or who were taking drugs such as ketoconazole or glucocorticoids. Testosterone levels from the entry visit were compared with a visit on average six months before the visit in which wasting-defining weight loss was observed. The bioavailable testosterone was significantly decreased at the time of the visit before the visit in which wasting was clear (Figure 5) (56).

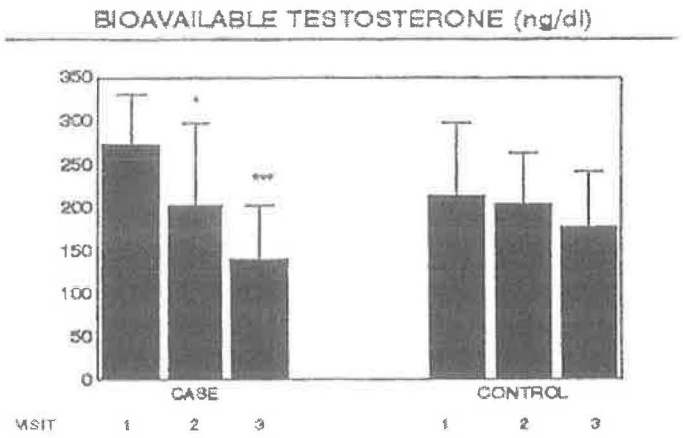

Figure 5. Bioavailable testosterone levels in men who experienced HIV wasting (cases) and HIV controls at enrollment visit (visit 1), visit immediately before wasting (visit 2), and the visit at which wasting was first documented.

Although the weight loss characteristic of AIDS wasting is no doubt multifactorial (see below), these data suggest that testosterone deficiency may contribute to it. In 58 HIV men who were asymptomatic for manifestations related to AIDS, bioavailable testosterone was assessed in relation to the CD4 count (57). Patients with clinical or biochemical signs of liver disease or thyroid illness, drug users and excessive alcohol consumers were not included. None had persistent hepatitis B or were infected with hepatitis C. None received ketoconazole, rifampin, opiates, or phenytoin. Group 1 had CD4 > 500, group 2 CD4 350-500, group 3 CD4 200-349, and group 4 CD4 < 200. Compared to an age-related healthy HIV negative control group, all patient groups had significantly elevated SHBG levels and significantly lower bioavailable testosterone levels Table 2 (57). Total testosterone levels were only significantly lower than controls in group 4.

Table 2. Testosterone, bioavailable testosterone and SHBG serum levels (nmol/l) in controls and HIV-infected patients.

	N	Testosterone	Bioavailable Testsoterone	SHBG
Controls	11	22.6 ± 4.2	10.4 ± 3.4	22.9 ± 4.2
CD4 > 500	14	22.4 ± 8.1	7.2 ± 3.4*	32.6 ± 9.3**
CD4 350-500	16	22.6 ± 7.6	6.2 ± 2.9**	35.9 ± 12.5**
CD4 200-349	22	21.2 ± 7.4	5.7 ± 2.7***	37.2 ± 17.2**
CD4 < 200	6	16.2 ± 4.6*	3.8 ± 1.2***	35.4 ± 11.4*

Mean ± SD; * P<0.05, ** P<0.01, *** P<0.001 vs controls

The CD4 counts were correlated significantly with the bioavailable testosterone levels but not the total testosterone levels (57). LH levels were not abnormal is this study. Another study in which men were followed for four years found that during the course of

progression to AIDS there was a transient period in which LH levels increased before they returned to normal and testosterone fell (58). This was interpreted by the authors as being consistent with a stage of partially compensated primary hypogonadism. In studies of testicular tissue of AIDS patients obtained at autopsy, decreased spermatogenesis, fibrosis of the interstitium, and mild to moderate inflammation with predominantly mononuclear cells surrounding the tubules was noted (58). A significant negative correlation was observed between the score of interstitial inflammation and serum testosterone.

Cytokines likely play a major role in the weight loss and decreased testosterone seen in HIV patients. In the age of highly active antiretroviral therapy (HAART), the incidence of most of the complications associated with HIV infection has declined in the developed world. However, the metabolic derangements associated with HIV infection have not been eliminated. Even though severe weight loss (wasting syndrome) appears to be less common today, erosion of lean body mass (LBM) is still evident in many patients when body composition is measured (59). These authors wanted to evaluate HIV patients to see if loss of lean body mass (cachexia) can occur even without a loss of weight as they had shown for rheumatoid arthritis patients (see below). They sought to determine whether either testosterone or the catabolic cytokines are important factors in regulating weight, body composition, or metabolic rate in HIV-infected adults in the absence of overt wasting. A subset of the 695 men in the Tufts Nutrition for Healthy Living Study who were having their body composition and resting energy expenditure measured every six months also had blood samples obtained for peripheral blood mononuclear cell cytokine production. The primary goal was the longitudinal analysis of change in LBM in these 170 men after the date of cytokine production measurement. The prevalence of low free testosterone in these men was 17.5%. There was a significant inverse linear relationship between change in LBM and TNF-α and IL-1β production. There was a significant inverse linear relationship between free testosterone and TNF-α and IL-1β production ($P < 0.02$ for each). In a multivariate linear regression model that contained cytokines and testosterone, TNF-α and testosterone were both associated with the change in resting energy expenditure (REE) after adjusting for multiple other variables. The incidence of classical AIDS wasting in this cohort was less than 2% with 43% taking HAART. However, over one-third of patients lost $\geq$ 1 kg and 12% lost > 5 kg of LBM over an average follow-up of 8 months, and 23% lost $\geq$ 2 kg of weight. In contrast to groups of men with AIDS wasting and marked testosterone deficiency, in this less severely affected group no independent affect of serum free testosterone on change in LBM or REE could be demonstrated after adjusting for other variables. [It should be noted that this study used a free testosterone analog assay that is not felt to be as reliable as the other methods for estimating free testosterone.]

The benefit of testosterone replacement therapy in men with the AIDS wasting syndrome and low free testosterone was assessed in a randomized, double-blind, placebo-controlled six month trial in 51 patients (60). Compared with patients who received placebo, testosterone-treated patients gained significant amounts of fat-free mass, lean body mass, and muscle mass (Figure 6). Patients who received testosterone reported benefit from the treatment with significant improvement in feeling better, perceived quality of life, and

improved appearance. Changes in weight, fat mass, total body water, and exercise functional capacity did not significantly differ between the groups.

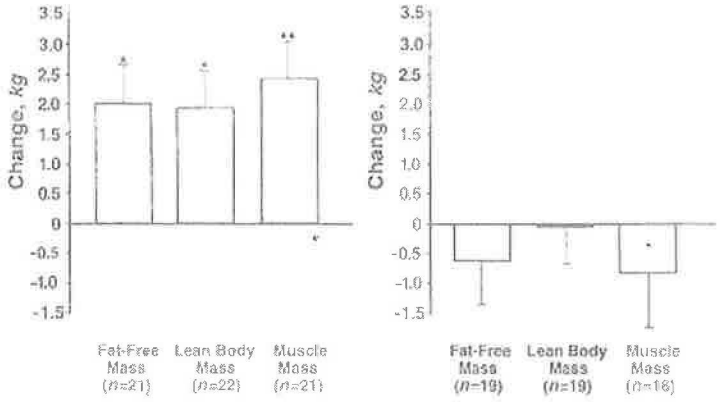

Figure 6. Mean change ± SE for fat-free mass, lean body mass, and muscle mass in patients who received testosterone (left) and patients who received placebo (right) for 6 months. * $P < 0.05$, ** $P < 0.01$ for the change from baseline between groups.

In an open-label administration follow-up study of these same subjects, subjects initially randomized to testosterone continued to gain LBM during open-label administration (2.0 kg during 0-6 months versus 1.6 kg during 6-12 months) (61). Bhasin and colleagues evaluated whether resistance exercise could add to the benefit of testosterone replacement in HIV infected men with weight loss and low or low-normal testosterone (< 349 ng/dl) in regard to muscle strength and weight gain in a four month study (62). Testosterone and resistance exercise promoted gains in body weight, muscle mass, muscle strength, and lean body mass; however, testosterone and exercise did not produce greater gains than either intervention alone.

Testosterone deficiency may be associated with a number of nonspecific symptoms including depression. Further study by Grinspoon and colleagues identified an increased depression score (Beck Depression Inventory) in association with hypogonadism in men with AIDS wasting, independent of weight, virologic status, and other disease factors (63). In such patients, administration of testosterone in replacement doses resulted in a significant improvement in depression inventory score. This effect may be a direct effect of testosterone or related to the positive effect of testosterone on weight or change in appearance.

Chronic Lung Disease

There are probably at least three mechanisms for the testosterone deficiency seen in some men with chronic lung disease: chronic hypoxia, glucocorticoid therapy, and inflammatory cytokines (64).

The apparent effect of chronic hypoxia on the H-P-T axis was mentioned above in the description of a patient with severe obesity and the Pickwickian syndrome. Semple and colleagues have several reports of men with hypoxemia associated with chronic obstructive pulmonary disease (COPD), unstable cor pulmonale, or pulmonary fibrosis in which there is a significant correlation of serum testosterone levels with arterial oxygen tensions (65-67). In most men serum LH levels were not elevated, whereas a minority had elevated LH levels. In his summary figure of the relation of testosterone and $Pa0_2$ about half had low serum testosterone levels (67).

Kamischke and colleagues investigated the relationship between testosterone deficiency and corticosteroid use (68). Thirty six men with COPD of whom 16 were receiving oral glucocorticoid medication (mean dose 9.4±1.1 mg prednisolone) were investigated in a cross-sectional cohort study. Patients with and without oral glucocorticoid therapy were not different in terms of age, smoking history and additional therapy. Vital capacity, FEV1, airway resistance, intrathoracic gas volume, and blood gases at rest were not different between the groups. Free testosterone levels were decreased in 45% of men not receiving steroids and 100% of those taking steroids. In patients receiving glucocorticoids free testosterone levels were significantly correlated with the current glucocorticoid dosage ($r = -0.504$; $p=0.007$) (Figure 7) (68).

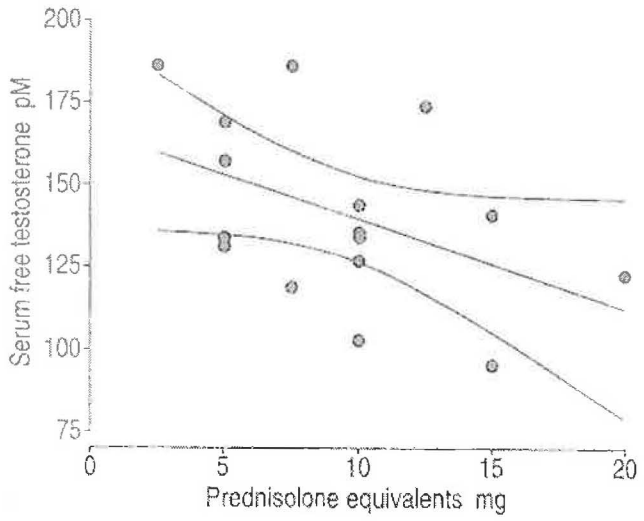

Figure 7. Daily oral glucocorticoid dose expressed as prednisolone equivalents versus serum free testosterone in 16 patients with COPD treated with prednisolone. 200 pM is the lower limit of normal for free testosterone. The regression line and 95% confidence limits are shown.

A prior study 10 years earlier made similar observations of a significant negative correlation of glucocorticoid dose and serum testosterone (69). In each of these studies serum LH levels were normal. Thus glucocorticoid therapy appears to aggravate hypogonadism in these men with COPD. However, almost half of patients have low free testosterone in the absence of glucocorticoid treatment.

Similar to patients with HIV infection, men with chronic lung disease may have increased REE and decreased LBM associated with inflammatory cytokines in their serum (70). Diminished muscle function is commonly the result of muscle wasting in COPD; its prevalence increases from 20% in clinically stable outpatients up to 35% in patients presenting for pulmonary rehabilitation (64). Selective wasting of LBM with preservation of fat mass has been observed so that it is possible to have loss of peripheral muscle mass in the setting of a normal BMI (71). Inflammatory cytokines may contribute to muscle wasting through the inhibition of myogenic differentiation via an NF-κB dependent pathway (reviewed in 72). In a study of 45 men with COPD in which mid-thigh muscle cross-sectional area was used as a marker for severity of LBM loss, IL-6 levels were significantly negatively correlated with bioavailable testosterone levels (73). In men with the more severe LBM loss (mid-thigh muscle cross-sectional area $<70cm^2$) the ratio of IL-6 to bioavailable testosterone was increased compared to men with less severe muscle loss. Finally, changes in leptin with COPD acute exacerbations may contribute to decreases in LBM (74). In animals administration of TNF-α or IL-1 results in increased circulating leptin concentrations (75). In patients admitted with a COPD exacerbation serum leptin was six-fold elevated on day 1compared to healthy subjects and remained five-fold elevated on day 7 of hospitalization (74). Presumably, elevated leptin would suppress dietary intake. Dietary intake in these subjects had decreased just before admission and increased gradually during hospitalization. These same authors had previously shown that in stable patients with COPD dietary intake was inversely related to plasma leptin (76). As with HIV infection it may be difficult to differentiate the cause of loss of LBM between a direct effect of cytokines on REE versus an indirect effect of lower testosterone levels.

There are a number of studies reporting the benefit of androgen therapy in COPD in regard to increase in LBM (77-80) and at least one reporting significantly increased maximal inspiratory mouth pressure (77). Unfortunately all of these studies involve the administration of anabolic steroids rather than testosterone itself, and there is no attempt to select for men with low testosterone. In one report the authors note that the 12 of the 30 men who had a low baseline testosterone gained 6.25 ± 0.92 lb of LBM compared to 3.17 ± 2.68 lb for the remainder with normal testosterone (79). Finally, in the one study that looked at the differences between men who were receiving or not receiving glucocorticoids, greater improvements in maximal inspiratory strength ($p = 0.046$) and peak work load ($p = 0.023$) were seen in the men receiving glucocorticoids (80).

Rheumatoid Arthritis

Testosterone levels may be low in men with rheumatoid arthritis (81-88). In most studies the gonadotropin levels have been normal, but in one study both LH and FSH levels were increased significantly compared to age matched control men or men with ankylosing spondylitis (81). In further support of a primary problem with the testis in some men, a study comparing men with rheumatoid arthritis to men with osteoarthritis found that the response to hCG was significantly decreased (82). In general the free or bioavailable testosterone levels were more consistently lower in the rheumatoid arthritis patients than

were the total testosterone levels (81, 83, 86, 88). The frequency of a low bioavailable testosterone concentration in the largest study of 104 men was 32% compared with 7% in the 99 age-matched control subjects ($P<0.001$) (88). These men were not acutely ill and were being followed in an out patient clinic with usual treatment. In this study treatment with glucocorticoids or other medications did not appear to influence the bioavailable testosterone. However, in other studies glucocorticoid therapy was associated with significantly lower testosterone levels (85, 86) and lower LH levels (85). Thus rheumatoid arthritis is similar to COPD in that low dose prednisone can add to the effect of the disease process itself in suppressing the H-P-T axis. Men who have acute flares in disease activity requiring hospitalization have even lower testosterone levels that remain suppressed for a prolonged period (84).

Similar to HIV infection and COPD, there is evidence for a cytokine-driven hypermetabolism in rheumatoid arthritis (RA) with chronic inflammation leading to a reduced body cell mass (89). In an important study 23 RA patients and 23 healthy subjects matched for age, sex, race, and weight, body cell mass was 13% lower ($P < 0.00001$), resting energy expenditure was 12% higher ($P < 0.008$), and physical activity was much lower ($P < 0.001$) in subjects with RA. Production of TNF-α and IL-1β was significantly higher in RA patients compared with controls. In multivariate analysis, cytokine production was directly associated with resting energy expenditure in RA subjects ($P < 0.001$). Energy intake in RA subjects was inversely associated with IL-1β production ($P < 0.005$). Adjuvant arthritis in rats provides an animal model for this inflammatory cachexia similar to RA in humans (90).

There is some disagreement in the interpretation of the low testosterone levels in men with rheumatoid arthritis (91). It is known that autoimmune disease is much less common in men compared to women, and men with congenital hypogonadism (e.g., Klinefelter's syndrome) have an increased likelihood of developing autoimmune diseases. Moreover, there are androgen receptors in macrophages and synoviocytes, and androgen treatment of macrophages and synoviocytes *in vitro* results in suppression of IL-1β and IL-6 production (92, 93). An interesting aside is that cyclosporine A, which has immune suppressive effects in autoimmune diseases and causes increased body hair, has been shown to increase 5α-reductase activity in synovial macrophages and increase serum levels of 3α-androstanediol glucuronide levels in treated patients (94, 95). This has led some authorities to postulate that the high prevalence of low testosterone in men with RA merely reflects that it is a risk factor for developing RA and not a result of the inflammatory state. A nested case-control study of a cohort of 19,072 Finnish adults provides some data to refute this concept (96). The cohort had neither arthritis nor a history of it during baseline evaluations in 1973-1977. Three matched controls were selected for each of the 32 men who developed RA subsequently. Pre-illness serum testosterone levels were similar in patients and controls.

Surprisingly I could only find two reports of therapeutic trials of testosterone in men with RA. Neither of them is optimal. The first was an open trial of giving an oral testosterone ester not available in this country, testosterone undecanoate (97). It was uncontrolled and involved only seven men for six months. The IgM-RF and number of involved joints

decreased significantly. A subsequent randomized trial in 30 (15 placebo and 15 treated) men with RA noted a significant negative correlation at baseline between serum testosterone and both C reactive protein and sedimentation rate ($P < 0.01$ for each) (98). However, no effect of monthly injections of 250mg testosterone enanthate could be detected on disease activity at nine months. This dose of testosterone given monthly is likely inadequate replacement since testosterone levels fall to baseline two weeks after this dose in many men.

In summary, RA appears to be similar to HIV infection and COPD in that cytokine-mediated inflammation leads to losses in body cell mass associated with a negative impact on the H-P-T axis. Glucocorticoid therapy worsens the effects of the disease on the H-P-T axis. The fatigue and muscle weakness that may accompany testosterone deficiency coupled with the potential worsening of decreased bone mass already facilitated by the disease process would appear to make men with RA and decreased testosterone levels candidates for testosterone therapy.

Chronic Liver Disease

Chronic liver disease and chronic kidney disease (see below) are probably the two conditions that have been recognized for the longest time as being associated with testosterone deficiency in a significant fraction of patients. The combination of testicular failure and features of feminization in hepatic cirrhosis is well known (99, 100). Gynecomastia and testicular atrophy occur in half of men with cirrhosis. Loss of libido, impotence, and reduced sexual hair are frequently seen in men with chronic liver disease. Plasma estradiol levels are usually elevated, and testosterone levels are below normal in about 50% of patients. Levels of SHBG are increased two-fold or greater. The net result is a ratio in serum of unbound estradiol to unbound testosterone about 10 times normal. Spider nevi and palmar erythyema are attributed to hyperestrogenism. The mechanism of these changes has been evaluated (101-103). The metabolic clearance and production rates of testosterone are decreased, and estradiol production is increased. Extraglandular conversion of androgens, primarily the adrenal androgen precursor androstenedione, to estradiol and estrone is increased about three-fold, presumably because of decreased hepatic extraction of androgens.

Basal levels of LH and FSH range from normal to moderately elevated. Coupled with the finding of decreased testosterone production, the elevated gonadotropins are thought to indicate a primary testicular defect. This is generally related to the severity of the cirrhosis. In men with low testosterone levels, pulsatile LH secretion is impaired implying a defect at the hypothalamic-pituitary level (104, 105). When liver failure occurs gonadotropin suppression is superimposed. The presence of a primary testicular defect has been further confirmed by studies of hCG stimulation of serum testosterone (99, 100). The testosterone response was diminished in the men with cirrhosis. Although alcoholic cirrhosis has been studied primarily, hypogonadism is not related to the etiology of the cirrhosis (106).

There has been interest in the possible role of alterations of SHBG in some of the manifestations of cirrhosis. The metabolic clearance of testosterone is decreased but the metabolic clearance rate of estradiol is unchanged in men with cirrhosis and elevated SHBG. Studies indicate that SHBG from cirrhotic men selectively delivers estradiol, but not testosterone, to peripheral tissues of rats *in vivo* (107). Testosterone and estradiol may bind to different-charge isoforms of SHBG, and these may be altered in cirrhosis (108). This abnormality may result in the lack of decrease in estradiol metabolic clearance in cirrhosis. Whether relatively enhanced delivery of estradiol to peripheral tissues in cirrhosis has a bearing on gonadotropin secretion is not clear.

Cytokines are also elevated in chronic liver disease (109-112). TNF-α, IL-1β, and IL-6 are all significantly elevated in patients with chronic liver disease. In a study of 264 patients with various forms of chronic liver disease the percentage of patients with elevated cytokines was similar in those with and without cirrhosis (Figure 8) (110). Presumably, the increased cytokines could contribute to the defects in the H-P-T axis.

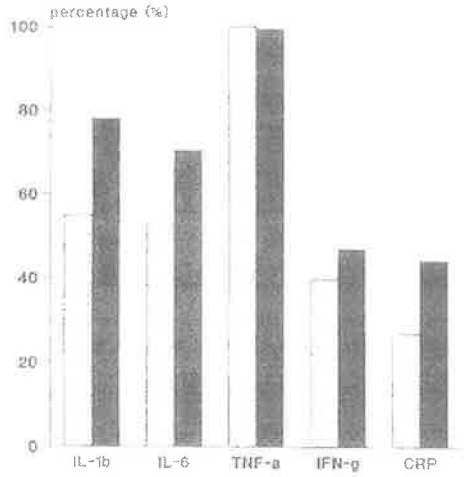

Figure 8. Percentage of patients with increased circulating cytokine and CRP levels in chronic liver disease (cirrhotic, black bars, n = 136; noncirrhotic, white bars, n = 128).

Liver cirrhosis is characterized by altered body composition and decreased muscle protein synthesis (113, 114). In a study of 18 male cirrhotics and 15 control subjects, fat mass and body cell mass were significantly decreased compared to controls ($P < 0.05$ and $P < 0.01$, respectively). Although resting energy expenditure was not measured, one might conjecture that it was likely increased due to the increased cytokines and that this accounts for the decreased body cell mass. Leptin levels, which are elevated in cirrhotic men when expressed per kilogram of fat mass, may also contribute to the decrease in body cell mass by suppressing appetite (114).

The effect of testosterone supplementation in men with cirrhosis has been studied in a few reports (115-118). The first of these involved the administration of free testosterone

intramuscularly every other day in 12 patients with cirrhosis compared with 9 controls treated conventionally. There was a reduction in ascites and pedal edema and subjective improvement in the testosterone-treated group (115), and serum albumin rose significantly by four weeks. Kley and colleagues primarily studied the effect of intramuscular testosterone enanthate on the androgen-estrogen imbalance in cirrhosis (116). Although estradiol levels increased (in correlation with the severity of the cirrhosis) after administration of testosterone, the estrogen/androgen ratio became normal. Whether the normalization of this ratio would be beneficial in regard to gynecomastia is unknown since this was a short term study. Another short term study compared various testosterone esters and oral micronized testosterone raising the testosterone level to 2000 to 4000 ng/dl for a month without any evidence of adverse effect (117). In this 28 day study it was not possible to adequately assess possible beneficial effects. Finally, in a double-blind placebo-controlled multicenter trial of oral micronized testosterone, patients were followed for a median of 28 months (118). Although the prevalence of gynecomastia decreased significantly, there was no beneficial effect of testosterone on survival. Although one would think that there might be concern for using anabolic steroids which have a known siginificant risk of hepatotoxicity, a report of the combination of nutritional support and oxandrolone in malnourished patients with severe alcoholic hepatitis found significant survival benefit by adding oxandrolone to nutritional support in patients with moderate malnutrition (119).

The effect of othotopic liver transplantation in men with end-stage liver disease on the changes noted above in the H-P-T axis has been studied (120). After successful transplantation in 10 men, all individuals had physiological levels of testosterone and free testosterone which increased twofold ($P < 0.01$) and tenfold ($P < 0.001$), respectively. Serum gonadotropin levels increased in the majority of patients, and estradiol and SHBG decreased significantly, ($P < 0.02$ and 0.01, respectively).

In summary, chronic liver disease is frequently associated with testosterone deficiency due to primarily a testicular defect but also with some evidence for hypothalamic-pituitary dysfunction. Estrogen production is increased due to altered clearance of adrenal androgens by the liver. Increased cytokines and leptin may contribute to a decreased body cell mass. Testosterone therapy may return the estrogen to androgen ratio toward normal and improve gynecomastia.

Chronic Kidney Disease

Men with chronic renal insufficiency have clinical features of testosterone deficiency including some features of feminization, but the changes are usually less florid than in men with cirrhosis (121, 122). The changes in testicular function are usually similar, that is, primary testicular failure with elevated gonadotropins and low testosterone levels. Two-thirds of men on chronic hemodialysis have low testosterone levels. About half of men undergoing dialysis for renal failure experience decreased libido and impotence. Gynecomastia is now less common among uremic men because dialysis intensity and nutrition have improved. The mechanism for the gynecomastia is decreased testosterone levels. Plasma testosterone production rates are decreased. The response of plasma

testosterone to acute hCG stimulation is subnormal, whereas the testosterone level can be increased to normal with chronic hCG treatment. SHBG levels are unchanged. The clearance of LH is decreased, and thus high levels can accumulate. The LH to FSH ratio is increased, and LH levels are elevated early in renal insufficiency (GFR 30-50 ml/min). The levels rise with decreasing renal function but do not reach the castrate range. The degree of elevation of LH levels in uremic men suggests diminished hypothalamic-pituitary responsiveness to lowered testosterone levels and impaired regulation of gonadotropin secretion. Bioassays of LH, measured by *in vitro* Leydig cell bioassay, are increased with the bioactive to immunoactive ratio similar to eugonadal men but higher than nonuremic men with primary testicular failure. Studies of LH isoforms in men on dialysis indicate that more basic isoforms are present in uremic men and that the degree of shift to more basic isoforms correlates with lesser bioactivity and consequently with lower testosterone levels (123). Pulsatile LH secretion is reduced in uremic men implying a reduction in the firing of the hypothalamic GnRH pulse generator. LH response to exogenous GnRH is excessive, delayed, and prolonged.

Hyperprolactinemia due to a three-fold or greater increase in PRL secretion rather than impaired clearance (reduced by only 33%) is common in uremia. Enhanced secretion is mainly due to blunted lactotrope sensitivity to acute dopaminergic inhibition (124). Prolactin levels rise proportionately with creatinine. Hyperprolactinemia and abnormal prolactin regulation are not corrected by dialysis.

Although hemodialysis results in only minor improvements in the H-P-T axis abnormalities in end stage renal disease, successful renal transplantation results in reversal of the changes in the majority of men (125, 126). Testosterone levels increase, and LH levels decrease somewhat but not to normal. Sexual function improves in most men. Residual hypogonadism correlated with duration of dialysis before transplantation of longer than one year ($P < 0.01$) (126). Hyperprolactinemia and abnormal prolactin regulation completely resolve after successful renal transplantation (124).

Inflammatory cytokine-mediated increases in resting energy expenditure and decreases in lean body mass occur in chronic renal failure patients (127-129). Increased levels of serum TNF-α and IL-1β did not differ significantly between undialyzed patients with chronic renal failure and patients on either chronic hemodialysis or chronic ambulatory peritoneal dialysis (127). In a study of 230 end stage renal disease subjects serum levels of TNF-α, Il-1β, and IL-6 were each on average 7 to 9 times normal (128). Increased leptin levels are found in renal failure (reviewed in 129) and could contribute to poor nutritional intake. Presumably, the elevated inflammatory cytokines could have a direct toxic effect on Leydig cell function, although this has not been specifically evaluated in chronic renal failure.

For many years, androgens, specifically anabolic steroids, were standard therapy in end stage renal disease patients to treat the anemia (130-132). In the late 1980s when recombinant human erythropoietin (EPO) became available, use of androgen for these purposes became uncommon. The adverse virilizing effects of androgens make their use for this purpose in women and children unacceptable. However, for selected patients,

particularly in countries with limited health care resources, androgen therapy continues to be used with similar success to EPO. Given that six months of nandrolone decanoate, a commonly used anabolic steroid to treat anemia in dialysis patients, costs $350 versus as much as $5750 for EPO therapy for the same time, it is easy to see how this could be the treatment of choice in men. The risk of increased blood pressure is less with nandrolone compared to EPO therapy. Moreover, several studies have shown a benefit to combining androgen with low dose EPO (reviewed in 132). In one prospective randomized trial the combination was shown to be superior to EPO alone. The mechanism of action of androgens on erythropoiesis is thought to be both a stimulation of EPO and direct effects on stem cells (reviewed in 132).

Of greater interest to the current discussion is whether replacement testosterone might be beneficial to the malnutrition and decreased muscle mass and strength that are common in these patients and correlate with increased mortality and adverse disease outcomes (reviewed in 133). Singh and colleagues have done a short term (28 day) study to assess whether the pharmacokinetics of a transdermal testosterone system is the same in men on chronic hemodialysis as in healthy hypogonadal men. Two testosterone patches were able to maintain midnormal total and free testosterone levels in men on hemodialysis similar to the control men (133). There is one randomized controlled trial of nandrolone decanoate in dialysis patients (134). Lean body mass increased significantly in patients given nandrolone compared with patients given placebo. This effect was significantly greater than the change in lean body mass in the placebo group (Figure 9) (134).

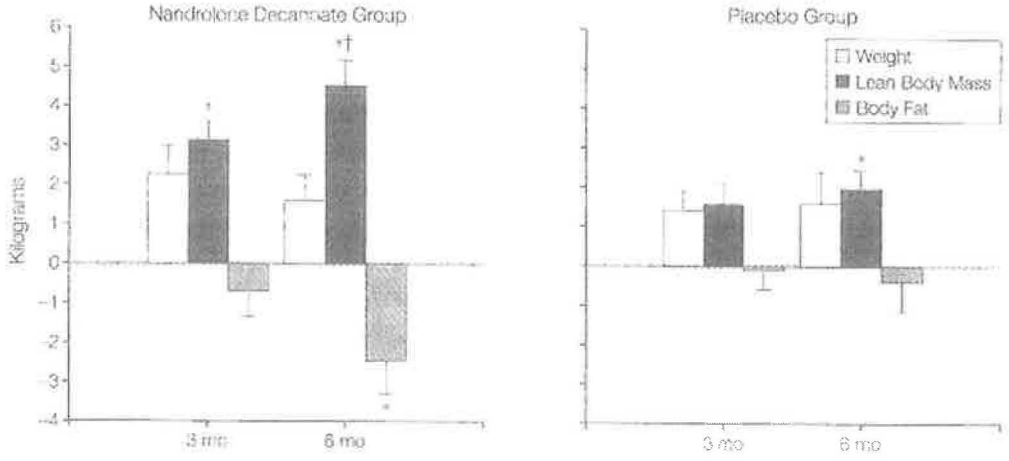

Figure 9. Changes in weight and body composition. Body composition measured by DEXA. Changes from baseline values expressed as mean ± SEM. Asterisks indicate statistical significance compare with baseline values ($P < 0.05$); dagger, significance compared with the placebo group ($P < 0.01$).

Serum creatinine values increased in the nandrolone group ($P = 0.02$) but not in the placebo group, suggesting an increase in muscle mass. Time to complete the walking and the stair climbing test decreased from 36.5 to 32.7seconds in the nandrolone group, while

those in the placebo group increased from 38.7 to 42.1 seconds (P = 0.05). Since nandrolone is an anabolic steroid and must be given parenterally, a study of testosterone itself would be useful to evaluate the possible benefits in regard to increased muscle mass and functional capacity.

Opioid Treatment of Chronic Non-Malignancy Pain

The evaluation of complaints of loss of libido and erectile dysfunction in male narcotic addicts using heroin or methadone led to the observation that testosterone levels were decreased (135, 136). The testosterone levels were decreased to a lesser extent in heroin users than in men on a methadone treatment program. The authors speculated that methadone has a slower clearance from the body and thus provides more consistent levels than the rapid fluctuations seen with heroin use. A better understanding of the consequences of chronic opioid treatment has come from the studies of patients treated with either sustained-action oral opioids or intrathecal opioids for chronic non-malignancy pain (137-139). Chronic nonmalignant pain, persisting more than six months, affects 15-30% of the population. The majority of chronic pain patients respond to a combination of physical modalities and nonopioid analgesics. However, approximately 20% of these patients do not derive sufficient pain relief from traditional measures and may benefit from therapy with opioids. Recently the intrathecal route has become a popular alternative way to administer opioids; a 30 times lower dose is sufficient to obtain a comparable pain relief to systemic administration. However, side effects are not eliminated. Whether opioids are administered orally or intrathecally the low testosterone is associated with low LH levels in keeping with the observation that opiodergic neurons are involved in the negative feedback inhibition of androgens at the hypothalamic level to inhibit GnRH secretion. Opioids stimulate prolactin secretion, and thus one might postulate that the secondary hypogonadism was due to prolactin excess. However, with the chronic administration of opioids prolactin levels are not increased (137). Most men in these studies of chronic non-malignancy pain suffered from chronic back pain, many having undergone multiple cervical or lumbar spine operations. In the two studies of intrathecal opioids referenced, the number of men with low testosterone was 25 of 29 in the first study and 8 of 10 in the second (137, 138). The average testosterone level in the opioid treated men in each study was significantly lower than a control group matched chronic pain but not receiving opiates.

The final series is of men receiving oral sustained-action dosage forms of opioids several times daily. These were 54 community-dwelling outpatient men matched with control men with similar pain problems who were not receiving opioids. Although this study selected pain not related to malignancy, likely to avoid the problem of cachexia as a mechanism for low testosterone, presumably men receiving opioids for malignancy-related pain would have a similar response. Hormone levels averaged much lower in opioid users than in control subjects in a dose related-pattern ($P < 0.001$ for all comparisons) (Table 3) (139).

Table 3. Average Hormone Levels in Men Consuming Sustained-Action Opioids in Multiple Daily Doses.

Methadone Equivalents (mg)	N	Free Testosterone (nl 50-210 pg/ml)	Total Testosterone (nl 260-1,000 ng/dl)	Estradiol (nl 21-50 pg/ml)
0	27	127.4 ± 48.8	449.1 ± 181.1	32.0 ± 17.2
20-60	15	74.3 ± 43.5	265.8 ± 191.9	18.7 ± 8.4
70-120	23	41.7 ± 25.5	188.5 ± 193.4	14.7 ± 8.9
> 120	16	44.8 ± 26.3	172.1 ± 108.8	11.7 ± 6.3

For the purposes of this analysis hydrocodone 15mg, oxycodone 15mg, morphine sulfate 15mg, methadone 10mg, and codeine sulfate 100mg were considered to be equivalent. Free testosterone, testosterone, and estradiol levels were subnormal in 56%, 74%, and 74%, respectively, of opioid consumers. Of the 45 opioid-ingesting men who reported normal erectile function before opioid use, 39 (or 87%) reported severe erectile dysfunction or diminished libido after beginning their opioid therapy. Thus commonly prescribed opioids in sustained-action dosage forms usually produce subnormal sex hormone levels, which may contribute to a diminished quality of life for many patients with painful chronic illness. In the first series of men given intrathecal opioids, replacement therapy with testosterone was tried in 14 men with low testosterone with improvement in libido reported by 10 men. There are no reports of studies of testosterone supplementation in men on oral opioids with low testosterone.

Should Men with Chronic Illness and Low Testosterone Be Treated?

The symptoms of testosterone deficiency include relatively specific sexual symptoms such as diminished libido and erectile dysfunction as well as nonspecific symptoms including diminished energy, increased fatigue, depressed mood, diminished muscle mass and strength, diminished bone density, anemia, and impaired cognition. It is likely that most men with the chronic illnesses discussed above will have one or more of the nonspecific symptoms. The average frequency of testostosterone deficiency in these groups of men is about 50%. Thus, it would appear to be reasonable to recommend measuring bioavailable or free testosterone in most men with these chronic illnesses. The next question is then whether the risk/benefit ratio favors treatment. The potential benefit in these various conditions varies with the individual illnesses (see below).

The potential risks of testosterone replacement therapy and the conclusions expressed in a recent review (140) regarding their likelihood are:

a) sleep apnea—infrequent
b) acne or oily skin—infrequent
c) gynecomastia—rare, usually reversible
d) cardiovascular disease—existing evidence suggests neutral or possible beneficial effect
e) lipid alterations—most studies show no change with physiologic replacement

f) erythrocytosis—common with injections; requires monitoring
g) fluid retention—rarely of significance
h) hepatotoxicity—limited to oral 17α-alkylated anabolics which are not recommended
i) testicular atrophy or infertility—common in young men; usually reversible with cessation of treatment
j) benign prostatic hyperplasia—rarely of clinical significance
k) prostate cancer—controversial; unknown level of risk; requires long-term monitoring

The risk of stimulating the growth of an unrecognized prostate cancer is greatest in older men. Thus many investigators have been frustrated by the decision of the VA and an advisory panel not to pursue the large long-term controlled trial of testosterone replacement in elderly men with partial androgen deficiency that would be required to assess this risk. We are unlikely to have an answer to this major risk concern for a very long time. In certain chronic illnesses there is a predisposition to one or more of the risks of testosterone replacement. In COPD patients with polycythemia, worsening erythrocytosis could pose a problem with risk for stroke. Very obese men already at risk for obstructive sleep apnea would be more likely to suffer this adverse effect.

The benefit of physiological replacement of testosterone in men with AIDS in regard to lean body mass is clear and should apply to men with other conditions associated with cachexia or frank wasting such as chronic lung disease, rheumatoid arthritis, and ESRD on dialysis. The improvement in sexual function, general well-being, and energy should benefit all affected men. Increased muscle strength should lessen the impact of the joint problems of rheumatoid arthritis patients and make it more feasible to exercise. In men with COPD increased muscle strength might improve breathing.The benefits in regard to decreasing gynecomastia in cirrhotics and improving the hematocrit in dialysis patients were mentioned above.

Decisions about treatment will need to be made on an individual basis. The potential risks and benefits should be discussed with the patient. If there are only nonspecific symptoms (fatigue, weakness, depression) and the lowering of testosterone is equivocal, consideration can be given to a trial to see if therapy is beneficial in relieving symptoms. The specific recommendations for monitoring for potential adverse effects are given in the recent review cited above (140). The most physiologic forms of testosterone replacement are the transdermal preparations. The available testosterone patch has a significant risk of skin irritation whereas the testosterone gels have a much lower incidence of this problem (140).

References:

1. Griffin JE, Wilson JD 2003 Disorders of the testis and male reproductive tract. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS (eds). Williams Textbook of Endocrinology. 10th Ed. Saunders, Philadelphia, pp 709-770
2. Veldhuis JD, Rogol AD, Samojlik E, Ertel NH 1984 Role of endogenous opiates in the expression of negative feedback actions of androgen and estrogen on pulsatile properties of luteinizing hormone secretion in man. J Clin Invest 74: 47-55
3. Hayes FJ, DeCruz S, Seminara SB, et al 2001 Differential regulation of gonadotropin secretion by testosterone in the human male: absence of a negative feedback effect of testosterone on follicle-stimulating hormone secretion. J Clin Endocrinol Metab 86: 53-58
4. Akima RS, Flier JS 2000 Leptin. Ann Rev Physiol 62: 413-437
5. Mann DR, Johnson AOK, Gimpel T, Castracane VD 2003 Changes in circulating leptin, leptin receptor, and gonadal hormones from infancy until advanced age in humans. J Clin Endocrinol Metab 88: 3339-3345
6. Cohen PE, Hardy MP, Pollard JW 1997 Colony-stimulating factor-1 plays a major role in the development of reproductive function in male mice. Mol Endocrinol 11: 1636-1650
7. Pardridge WM 1986 Serum bioavailability of sex steroid hormones. Clin Endocrinol Metab 15: 259-278
8. Vermeulen A, Verndonch L, Kaufman JM 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 84: 3666-3672
9. Matsumoto AM, Bremner WJ 2004 Editorial: serum testosterone assays—accuracy matters. J Clin Endocrinol Metab 89: 520-524
10. Wang C, Catlin DH, Demers LM, et al 2004 Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. J Clin Endocrinol Metab 89: 534-543
11. Bremner WJ, Vitiello MV, Prinz PN 1983 Loss of circadian rhythmicity in blood testosterone with aging in normal men. J Clin Endocrinol Metab 56: 1278-1281
12. Glass AR, Smith CE, Kidd GS, et al 1978 Response of the hypothalamic-pituitary-testicular axis to surgery. Fertil Steril 30: 560-563
13. Wang C, Chan V, Yeung RTT 1978 Effect of surgical stress on the pituitary-testicular function. Clin Endocrinol 9: 255-266
14. Wang C, Chan V, Tse TF, et al 1978 Effect of acute myocardial infarction on pituitary-testicular function. Clin Endocrinol 9: 249-253
15. Vogel AV, Peake GT, Rada RT 1985 Pituitary-testicular axis dysfunction in burned men. J Clin Endocrinol Metab 60: 658-664
16. Woolf PD, Hamill RW, McDonald JV et al 1985 Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 60: 444-450
17. Lephart ED, Baxter CR, Parker CR Jr 1987 Effect of burn trauma on adrenal and testicular steroid hormone production. J Clin Endocrinol Metab 64: 842-848
18. Luppa P, Munker R, Nagel D, et al 1991 Serum androgens in intensive-care patients: correlations with clinical findings. Clin Endocrinol 34: 305-310
19. Dong Q, Hawker F, McWilliam D, et al 1992 Circulating immunoreactive inhibin and testosterone levels in men with critical illness. Clin Endocrinol 36: 399-404
20. Spratt DI, Cox P, Orav J, et al 1993 Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab 76: 1548-1554
21. Spratt DI, Bigos ST, Beitins I, et al 1992 Both hyper- and hypogonadotropic hypogonadism occur transiently in acute illness: bio- and immunoactive gonadotropins. J Clin Endocrinol Metab 75: 1562-1570
22. Nierman DM, Mechanick JI 1999 Hypotestosteronemia in chronically critically ill men. Crit Care Med 27: 2418-2421
23. Van den Berghe G, Weekers F, Baxter RC, et al 2001 Five-day pulsatile gonadotropin-releasing hormone administration unveils combined hypothalamic-pituitary-gonadal defects underlying profound hypoandrogenism in men with prolonged critical illness. J Clin Endocrinol Metab 86: 3217-3226

24. Williams CL, Nishihara M, Thalabard J-C, et al 1990 Corticotropin-releasing factor and gonadotropin-releasing hormone pulse generator activity in the rhesus monkey. Neuroendocrinol 52: 133-137
25. Barbarino A, De Marinis L, Tofani A, et al 1989 Corticotropin-releasing hormone inhibition of gonadotropin release and the effect of opioid blockade. J Clin Endocrinol Metab 68: 523-528
26. Metzger DL, Kerrigan JR, Rogol AD 1997 The short-term infusion of ovine corticotropin-releasing hormone does not alter luteinizing hormone concentrations in young adult men. J Clin Endocrinol Metab 82: 697-700
27. Refojo D, Arias P, Moguilevsky JA, Feleder C 1998 Effect of bacterial endotoxin on in vivo pulsatile gonadotropin secretion in adult male rats. Neuroendocrinol 67: 275-281
28. Damas P, Reuter A, Gysen P, et al 1989 Tumor necrosis factor and interleukin-1 serum levels during severe sepsis in humans. Crit Care Med 17: 975-978
29. Baigrie RJ, Lamont PM, Kwiatkowski D, et al 1992 Systemic cytokine response after major surgery. Brit J Surg 79: 757-760
30. Tsigos C, Papanicolaou DA, Kyrou I, et al 1999 Dose-dependent effects of recombinant human interleukin-6 on the pituitary-testicular axis. J Interferon Cytokin Res 19: 1271-1276
31. Corssmit EPM, Endert E, Sauerwein HP, Romijn JA 2000 Acute effects of interferon-α administration on testosterone concentrations in healthy men. Eur J Endocrinol 143: 371-374
32. Calkins JH, Sigel MM, Nankin HR, Lin T 1988 Interleukin-1 inhibits Leydig cell steroidogensis in primary culture. Endocrinology 123: 1605-1610
33. Mauduit C, Hartmann DJ, Chauvin MA, et al 1991 Tumor necrosis factor alpha inhibits gonadotropin action in cultured porcine Leydig cells: site(s) of action. Endocrinology 129: 2933-2940
34. Xiong Y, Hales DB 1993 The role of tumor necrosis factor-α in the regulationof mouse Leydig cell steroidogenesis. Endocrinology 132: 2438-2444
35. Orava M, Cantell K, Vikho R 1985 Human leukocyte interferon inhibits human chorionic gonadotropin stimulated testosterone by porcine Leydig cells in culture. Biochem Biophys Res Comm 127: 809-815
36. Lin T, Hu J, Wang D, Stocco DM 1998 Interferon-γ inhibits the steroidogenic acute regulatory protein messenger ribonucleic acid expression and protein levels in primary cultures of rat Leydig cells. Endocrinology 139: 2217-2222
37. Mauduit C, Gasnier F, Rey C, et al 1998 Tumor necrosis factor-α inhibits Leydig cell steroidogenesis through a decrease in steroidogenic acute regulatory protein expression. Endocrinology 139: 2863-2868
38. Oglivie K, Rivier C 1998 The intracereboventricular injection of interleukin-1β blunts the testosterone response to human chorionic gonadotropin: role of prostaglandin- and adrenergic-dependent pathways. Endocrinology 139: 3088-3095
39. Oglivie KM, Hales KH, Roberts ME, et al 1999 The inhibitory effect of intracerebroventricularly injected interleukin 1β on testosterone secretion in the rat: role of steroidogenic acute regulatory protein. Biol Reprod 60: 527-533
40. Spratt DI 2001 Altered gonadal steroidogenesis in critical illness: is treatment with anabolic steroids indicated? Best Pract Res Clin Endocrinol Metab 15: 479-494
41. Gewasio JM, Dickerson RN, Swearingen J, et al 2000 Oxandrolone in trauma patients. Pharmacotherapy 20: 1328-1334
42. Smith SR, Chhetri MK, Johanson AJ, et al 1975 The pituitary-gonadal axis in men with protein-calorie malnutrition. J Clin Endocrinol Metab 41: 60-69
43. Chlebowski RT, Heber D 1982 Hypogonadism in male patients with metastatic cancer prior to chemotherapy. Cancer Res 42: 2495-2498
44. Aloi JA, Bergendahl M, Iranmanesh A, Veldhuis JD 1997 Pulsatile intravenous gonadotropin-releasing hormone administration averts fasting-induced hypogonadotropism and hypoandrogenemia in healthy, normal weight men. J Clin Endocrinol Metab 82: 1543-1548
45. Chan JL, Heist K, De Paoli AM, et al 2003 The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest 111: 1409-1421
46. Zumoff B, Strain GW, Miller LK, et al 1990 Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. J Clin Endocrinol Metab 71: 929-931

47. Giagulli VA, Kaufman JM, Vermeulen A 1994 Pathogenesis of the decreased androgen levels in obese men. J Clin Endocrinol Metab 79: 997-1000
48. Vermeulen A, Kaufman JM, Deslypere JP, Thomas G 1993 Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. J Clin Endocrinol Metab 76: 1140-1146
49. Schneider G, Kirschner MA, Berkowitz R, Ertel NH 1979 Increased estrogen production in obese men. J Clin Endocrinol Metab 48: 633-638
50. Tena-Sempere M, Pinilla L, Gonzalez LC, et al 1999 Leptin inhibits testosterone secretion from adult rat testis in vitro. J Endocrinology 161: 211-218
51. Caprio M, Isidori AM, Carta AR, et al 1999 Expression of functional leptin receptors in rodent Leydig cells. Endocrinology 140: 4939-4947
52. Isidori AM, Caprio M, Strollo F, et al 1999 Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 84: 3673-3680
53. Semple Pd'A, Graham A, Malcolm Y 1984 Hypoxia, depression of testosterone, and impotence in pickwickian syndrome reversed by weight reduction. Brit Med J 289: 801-802
54. Dobs AS 1998 Androgen therapy in AIDS wasting. Bailliere Clin Endocrinol Metab 12: 379-390
55. Grinspoon S, Corcoran C, Lee K, et al 1996 Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab 81: 4051-4058
56. Dobs AS, Few III WL, Blackman MR, et al 1996 Serum hormones in men with human immunodeficiency virus-associated wasting. J Clin Endocrinol Metab 81: 4108-4112
57. Laudat A, Blum L, Guechot J, et al 1995 Changes in systemic gonadal and adrenal steroids in asymptomatic human immunodeficiency virus-infected men: relationship with the CD4 cell counts. Eur J Endocrinol 133: 418-424
58. Salehian B, Jacobson D, Swerdloff RS, et al 1999 Testicular pathologic changes and the pituitary-testicular axis during human immunodeficiency virus infection. Endocr Pract 5: 1-9
59. Roubenoff R, Grinspoon S, Skolnik PR, et al 2002 Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. Am J Physiol Endocrinol Metab 283: E138-E145
60. Grinspoon S, Corcoran C, Askari H, et al 1998 Effects of androgen administration in men with the AIDS wasting syndrome. Ann Intern Med 129: 18-26
61. Grinspoon S, Corcoran C, Anderson E, et al 1999 Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. Clin Infect Dis 28: 634-636
62. Bhasin S, Storer TW, Javanbakht M, et al 2000 Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 283: 763-770
63. Grinspoon S, Corcoran C, Stanley T, et al 2000 Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. J Clin Endocrinol Metab 85: 60-65
64. Creutzberg EC, Casaburi R 2003 Endocrinological disturbances in chronic obstructive pulmonary disease. Eur Respir J 22: Suppl 46, 76s-80s
65. Semple PD, Watson WS, Beastall GH, Hume R 1980 Serum testosterone depression associated with hypoxia in respiratory failure. Clin Sci 58: 105-106
66. Semple Pd'A, Watson WS, Beastall GH, Hume R 1983 Endocrine and metabolic studies in unstable cor pulmonale. Thorax 38: 45-49
67. Semple Pd'A, Beastall GH, Brown TM, et al 1984 Sex hormone suppression and sexual impotence in hypoxic pulmonary fibrosis. Thorax 39: 46-51
68. Kamischke A, Kemper DE, Castel MA, et al 1998 Testosterone levels in men with chronic obstructive pulmonary disease wit or without glucocorticoid therapy. Eur Resp J 11: 41-45
69. MacAdams MR, White RH, Chipps BE 1986 Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 104: 648-651
70. Schols AMWJ, Buurman WA, Staal-van den Brekel AJ, et al 1996 Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 51: 819-824
71. Bernard S, Leblanc P, Whittom F, et al 1998 Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 158: 629-634
72. Wouters EFM 2002 Chronic obstructive pulmonary disease: systemic effects of COPD. Thorax 57: 1067-1070

73. Debigare R, Marquis K, Cote CH, et al 2003 Catabolic/anabolic balance and muscle wasting in patients with COPD. Chest 124: 83-89
74. Creutzberg EC, Wouters EFM, Vanderhoven-Augustin IML, et al 2000 Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease. Am J Resp Crit Care Med 162: 1239-1245
75. Sarraf P, Frederich RC, Turner EM, Ma G, et al 1997 Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J Exp Med 185: 171-175
76. Schols A, Creutzberg EC, Buurman WA, et al 1999 Plasma leptin is related to proinflammatory status and dietary intake in patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 160: 1220-1226
77. Schols AMWJ, Soeters PB, Mostert R, et al 1995 Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease: a placebo-controlled randomized trial. Am J Resp Crit Care Med 152: 1268-1274
78. Ferreira IM, Verreschi IT, Nery LE, et al 1998 The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 114: 19-28
79. Yeh SS, DeGuzman B, Kramer T 2002 Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. Chest 122: 421-428
80. Creutzberg EC, Wouters EFM, Mostert R, et al 2003 A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest 124: 1733-1742
81. Gordon D, Beastall GH, Thomson JA, Sturrock RD 1986 Androgenic status and sexual function in males with rheumatoid arthritis and ankylosing spondylitis. Q J Med 60: 671-679
82. Cutolo M, Balleari E, Giusti M, et al 1988 Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. Arthritis Rheum 31: 1314-1317
83. Spector TD, Perry LA, Tubb G, et al 1988 Low free testosterone levels in rheumatoid arthritis. Ann Rheum Dis 47: 65-68
84. Gordon D, Beastall GH, Thomson JA, Sturrock RD 1988 Prolonged hypogonadism in male patients with rheumatoid arthritis during flares in disease activity. Brit J Rheum 27: 440-444
85. Martens HF, Sheets PK, Tenover JS, et al 1994 Decreased testosterone levels in men with rheumatoid arthritis: effect of low dose prednisone therapy. J Rheumatol 21: 1427-1431
86. Mateo L, Nolla JM, Bonnin MR, et al 1995 Sex hormone status and bone mineral density in men wit rheumatoid arthritis. J Rheumatol 22: 1455-1460
87. Stafford L, Bleasel J, Giles A, Handelsman D 2000 Androgen deficiency and bone mineral density in men with rheumatoid arthritis. J Rheumatol 27: 2786-2790
88. Tengstrand B, Carlstrom K, Hafstrom I 2002 Bioavailable testosterone in men with rheumatoid arthritis—high frequency of hypogonadism. Rheumatology 41: 285-289
89. Roubenoff R, Roubenoff RA, Cannon JG, et al 1994 Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest 93: 2379-2386
90. Roubenoff R, Freeman LM, Smith DE, et al 1997 Adjuvant arthritis as a model of inflammatory chachexia. Arthritis Rheum 40: 534-539
91. Cutolo M, Seriolo B, Pizzorni C, Sullli A 2001 The role of androgens in rheumatic diseases. Isr Med Assoc J 3: 743-748
92. Li ZG, Danis VA, Brooks PM 1993 Effect of gonadal steroids on the production of IL-1 and IL-6 by blood mononuclear cells in vitro. Clin Exper Rheumatol 11: 157-162
93. Khalkhali-Ellis Z, Handa RJ, Price RH, et al 2002 Androgen receptors in human synoviocytes and androgen regulation of interleukin 1β (IL-1β) induced IL-6 production: a link between hypoandrogenicity and rheumatoid arthritis? J Rheumatol 29: 1843-1846
94. Giltay EJ, van den Borne BEEM, van Schaardenburg D, et al 1998 Androgenizing effect of low-dose cyclosporine in male patients with early RA. Brit J Rheumatol 37: 470-472
95. Cutolo M, Giusti M, Villaggio B, et al 1997 Testosterone metabolism and cyclosporine A treatment in rheumatoid arthritis. Brit J Rheumatol 36: 433-439
96. Heikkila R, Aho K, Heliovaara M, et al 1998 Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. Ann Rheum Dis 57: 281-285

97. Cutolo M, Balleari E, Giusti M, et al 1991 Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum 34: 1-5
98. Hall GM, Larbre JP, Spector TD, et al 1996 A randomized trial of testosterone therapy in males with rheumatoid arthritis. Brit J Rheumatol 35: 568-573
99. Van Thiel DH, Lester R, Sherins RJ 1974 Hypogonadism in alcoholic liver disease: evidence for a double defect. Gastroenterology 67: 1188-1199
100. Baker HWG, Burger HG, de Kretser DM, et al 1976 A study of the endocrine manifestations of hepatic cirrhosis. Q J Med 45: 145-178
101. Gordon GG, Olivo J, Rafii F, Southren AL 1975 Conversion of androgens to estrogens in cirrhosis of the liver. J Clin Endocrinol Metab 40: 1018-1026
102. Olivo J, Gordon GG, Rafii F, Southren AL 1975 Estrogen metabolism in hyperthyroidism and cirrhosis of the liver. Steroids 26: 47-56
103. Edman CD, MacDonald PC, Combes B 1975 Extraglandular production of estrogen in subjects with liver disease. Gastroenterology 69: 819 (Abstract)
104. Distiller LA, Sagel J, Dubowitz B, et al 1976 Pituitary-gonadal function in men with alcoholic cirrhosis of the liver. Horm Metab Res 8: 461-465
105. Bannister P, Handley T, Chapman C, Losowsky MS 1986 Hypogonadism in chronic liver disease: impaired release of luteinising hormone. Brit Med J 293: 1191-1193
106. Kaymakoglu S, Okten A, Cakaloglu Y, et al 1995 Hypogonadism is not related to the etiology of liver cirrhosis. J Gastroenerol 30: 745-750
107. Sakiyama R, Pardridge WM, Judd HL 1982 Effects of human cirrhotic serum on estradiol and testosterone transport into rat brain. J Clin Endocrinol Metab 54: 1140-1144
108. Terasaki T, Nowlin DM, Pardridge WM 1988 Differential binding of testosterone and estradiol to isoforms of sex hormone-binding globulin: selective alteration of estadiol binding in cirrhosis. J Clin Endocrinol Metab 67: 639-643
109. Khoruts A, Stahnke L, McClain CJ, et al 1991 Circulating tumor necrosis factor, interleukin-1 and interleukin-6 concentrations in chronic alcoholic patients. Hepatology 13: 267-276
110. Tilg H, Wilmer A, Vogel W, et al 1992 Serum levels of cytokines in chronic liver diseases. Gastroenterology 103: 264-274
111. Lee FY, Lu RH, Tsai YT, et al 1996 Plasma interleukin-6 levels in patients with cirrhosis: relationship to endotoxemia, tumor necrosis factor-α, and hyperdynamic circulation. Scand J Gatroenterol 31: 500-505
112. Genesca J, Gonzalez A, Segura R, et al 1999 Interleukin-6, nitric oxide, and the clinical and hemodynamic alterations of patients with liver cirrhosis. Am J Gastroenterol 94: 169-177
113. McCullough AJ, Bugianesi E, Marchesini G, Kalhan S 1998 Gender-dependent alterations in serum leptin in alcoholic cirrhosis. Gastroenterology 115: 947-953
114. Tessari P 2003 Protein metabolism in liver cirrhosis: from albumin to muscle myofibrils. Curr Opin Clin Nutr Metab Care 6: 79-85
115. Puliyel MM, Vyas GP, Mehta GS 1977 Testosterone in the management of cirrhosis of the liver—a controlled study. Aust N Z J Med 7: 596-599
116. Kley HK, Strohmeyer G, Kruskemper HL 1979 Effect of testosterone application on hormone concentrations of androgens and estrogens in male patients with cirrhosis of the liver. Gastroenterology 76: 235-241
117. Gluud C, Bennett P, Dietrichson O, et al 1981 Short-term parenteral and peroral testosterone administration in men with alcoholic cirrhosis. Scand J Gastroenterol 16: 749-755
118. The Copenhagen Study for Liver Diseases 1986 Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. Hepatology 6: 807-813
119. Mendenhall CL, Moritz TE, Roselle GA, et al 1993 A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a department of veterans affairs cooperative study. Hepatology 17: 564-576
120. Madersbacher S, Ludvik G, Stulnig T, et al 1996 The impact of liver transplantation on endocrine status in men. Clin Endocrinol 44: 461-466
121. Holdsworth S, Atkins RC, de Kretser DM 1977 The pituitary-testicular axis in chronic renal failure. N Engl J Med 296: 1245-1249
122. Handelsman DJ, Dong Q 1993 Hypothalamo-pituitary gonadal axis in men with chronic renal failure. Endocrinol Metab Clin N A 22: 145-161

123. Mitchell R, Bauerfeld C, Schaefer F, et al 1994 Less acidic forms of luteinizing hormone are associated with lower testosterone secretion in men on haemodialysis treatment. Clin Endocrinol 41: 65-73
124. Lim VS, Kathpalia SC, Frohman LA 1979 Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: reversal after transplantation. J Clin Endocrinol Metab 48: 101-107
125. Holdsworth SR, de Kretser DM, Atkins RC 1978 A comparison of hemodialysis and transplantation in reversing the uremic disturbance of male reproductive function. Clin Nephrol 10: 146-150
126. Handelsman DJ, Ralec VL, Tiller DJ, et al 1981 Testicular function after renal transplantation. Clin Endocrinol 14: 527-538
127. Pereira BJG, Shapiro L, King AJ, et al 1994 Plasma levels of IL-1β, TNFα and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. Kidney Int 45: 890-896
128. Kimmel PL, Phillips TM, Simmens SJ, et al 1998 Immunologic function and survival in hemodialysis patients. Kidney Int 54: 236-244
129. Pupim LB, Ikizler TA 2003 Uremic malnutrition: new insights into an old problem. Semin Dialysis 16: 224-232
130. Teruel JL, Marcen R, Navarro-Antolin J, et al 1996 Androgen versus erythropoietin for the treatment of anemia in hemodialyzed patients: a prospective study. J Am Soc Nephrol 7: 140-144
131. Teruel JL, Aguilera A, Marcen R, et al 1996 Androgen therapy for anaemia of chronic renal failure: indications in the erythropoietin era. Scand J Urol Nephrol 30: 403-408
132. Navarro JF, Mora C 2001 Androgen therapy for anemia in elderly uremic patients. Int Urol Nephrol 32: 549-557
133. Singh AB, Norris K, Modi N, et al 2001 Pharmacokinetics of a transdsermal testosterone systerm in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. J Clin Endocrinol Metab 86: 2437-2445
134. Johansen KL, Mulligan K, Schambelan M 1999 Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA 281: 1275-1281
135. Azizi F Vagenakis AG, Longcope C et al 1973 Decreased serum testosterone concentrations in male heroin and methadone addicts. Steroids 22: 467-472
136. Cicero TJ, Bell RD, Wiest WG, et al 1975 Function of the male sex organs in heroin and methadone users. N Engl J Med 292: 822-887
137. Abs R, Verhelst J, Maeyaert J, et al 2000 Endocrine consequences of long-term intrathecal administration of opioid. J Clin Endocrinol Metab 85: 2215-2222
138. Finch PM, Roberts LJ, Price L et al 2000 Hypogonadism in patients treated with intrathecal morphine. Clin J Pain 16: 251-254
139. Daniell HW 2002 Hypogonadism in men consuming sustained-action oral opioids. J Pain 3: 377-384
140. Rhoden EL, Morgentaler A 2004 Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 350: 482-492