IJPT
1735-2657/06/52-95-112
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 5:95-112, 2006

RIDR

REVIEW ARTICLE

Interrelationship between Androgen Levels, Ageing, and Cognitive Functions

HANUMANTHACHAR JOSHI and MILIND PARLE

For author affiliations, see end of text.

Received November 13, 2006; Accepted December 6, 2006

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

As men get older, there is a decline in functioning of many biological systems; the endocrine systems share such changes in hormone levels. Ageing in men is accompanied by progressive, but individually variable decline in serum testosterone production in healthy men especially in men over 60 years of age. Androgens determine the differentiation of male internal and external genitalia as well as the development and maintain ace of male secondary sex characteristics and male reproductive function. They have important metabolic effects on protein, carbohydrate and fat metabolism and contribute to the determination of muscle mass and strength and also affect behavior and cognition. In ageing men, the serum androgen levels are affected due to several factors such as , circadian rhythmicity, heredity, body mass, diet, stress, life style, smoking, alcohol, and exercise. The decreased levels androgen may lead to senile osteroporosis, hypogonadism, decreased libido and brain functions. The incidence of cognitive disorders such as dementia and Alzheimer's disease is also high in testosterone deficient adults. The relationship between endogenous plasma testosterone levels, visual-spatial orientation, depression and brain function plays a vital role while treating aged males with cognitive disorders associated with decline in testosterone levels. The present paper highlights various aspects of ageing associated decline in androgen levels, cognitive function and usefulness and risk of androgen replacement therapy in aged males.

Keywords: *Ageing, Androgen, Cognitive function*

Human evolution was characterized by a social structure in which mainly females gathered plants for sustenance, which were supplemented by hunting, much of it done by males [1]. This resulted in the selection for superior spatial skills associated with hunting in males, such as navigation and throwing accuracy [2,3], and selection for skills associated with gathering, such as object and location memory, in females [4].

Spatial research has yielded two patterns of sex differences: first, males outperform females in selected psychometric spatial tests [5] and second, males attend to cardinal and distance attributes and females attend to landmarks when reading a map or navigating [6, 7].

The influence of sex and age depends on the emergence of sex differences corresponds with puberty [8], whereas others maintain that differences exist earlier in development [9]. Based on a meta-analysis, sex differences in mental rotation tasks (i.e. tasks requiring one to mentally rotate objects in space) are found in young children whereas sex differences in spatial perception tasks (i.e., tasks requiring one to mentally maintain tial relationships while ignoring misleading cues) generally emerge by the age of 13 years [10]. Sex differences in location memory tasks are not found in children younger than 6 years, although differences have been reported in 10-year-olds and adolescents [11-13].

Men generally use more distances and cardinal directions, and women use more landmarks and relative directions [14-18]. There is some evidence that sex differences emerge soon after 9 years of age, with boys demonstrating a greater sense of orientation, and girls attending to more landmarks [16, 18-19]. Congruently, adolescent boys were found to use more directions when walking through a maze, whereas girls used more landmarks [20]. Females are better able to recall object locations, particularly under incidental learning situations, suggesting that females may be predisposed to implicitly encode object locations [44]. This female advantage has been replicated in children as young as 10 years, as well as across various types of stimuli, including those without verbal labels [21], supporting Eals and Silverman's [22] contention that location information is encoded non-verbally. In contrast, adult males have been found to be better at navigating in a novel environment

which lacked discernible landmarks, which was also found to be related to mental rotation performance on a psychometric task suggesting that a similar process underlies both tasks [2, 23].

Sex differences in object memory were found early in development, in children as young as 9 years. This is consistent with findings of a female advantage in prepubertal children [12, 22]. Location memory yielded a female advantage in the older children, but not in younger children, confirming the prediction that [4] female advantage emerges in adolescence, from 14years of age and onwards. At 12-13 years of age most girls enter puberty, characterized by increases in estrogen levels, a factor considered to significantly affect specific cognitive functioning [24]. The increase androgen levels accompanying puberty in males may enhance their performances in the male-biased tasks [22].

Sex-specific patterns of relationships between the spatial processes and route-learning strategies were also found. A particularly enlightening finding was the propensity for landmarks by females emerging later in development, at the age of 12, relative to the first emergence of sex differences in the three spatial processes. During adolescence, location memory, the spatial process deemed to be female-specific, was a significant factor for both preference variables, indicating that those with better location memory demonstrated greater landmark and relative direction preferences. The activational hormonal explanation would predict that spatial sex differences become exacerbated during puberty [25]. Results of spatial research have suggested that activational hormonal effects differentially affect the various spatial processes, with mental rotation being particularly sensitive to hormonal levels [23].

Aging in men is accompanied by a progressive, but individually variable decline of serum testosterone production, more than 20% of healthy men over 60 yr of age presenting with serum levels below the range for young men. Since antiquity, the importance of the testes for maintenance of virility, physical force, and male behavior has been recognized. Two hundred years before Christ, the Assyrians employed castration as a punishment for sexual offenses, whereas from antiquity eunuchs were employed by Orientals to take charge of their women. In the 8th century, the Chinese advocated the use of extracts of testicles for treatment of impotence [26]. Brown-Sequard [27-28] attributed the age-associated decline in physical and sexual performance to a decline in testicular function and claimed that he had experienced personally the evident beneficial effects on virility and well-being of the injection of tery) extracts of guinea pig and dog testes' effects.

Androgens are substances that determine the differentiation of male internal and external genitalia as well as the development and maintenance of male secondary sex characteristics and male reproductive function. Besides, they have important metabolic effects on protein, carbohydrate, and fat metabolism. Furthermore, androgens affect behavior and cognition. It is thus not surprising that age-associated phenomena such as a decline in virility and sexual activity, a decrease in muscle mass and strength, or an increased tendency to develop atherosclerosis and impairment of glucose metabolism have been related to an observed decline in testicular function in aging men.

Sex Steroids in the Systemic Circulation

Testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA), and its sulfate (DHEAS) are the major androgens in the systemic circulation. Testosterone is secreted almost exclusively by the testes, whereas only about 20% of circulating DHT originates from direct testicular secretion, the remainder being derived from reduction of testosterone in peripheral tissues [29]. Fifteen percent of plasma androstenedione originates from peripheral conversion of DHEA and testosterone, whereas 85% is secreted directly in approximately equal parts by the testes and the adrenals [30-31]; DHEA and DHEAS originate almost exclusively from the adrenals. Biologically, the most important plasma androgen is testosterone. It is largely bound to plasma proteins, only 1–2% being free, 40–50% being loosely bound to albumin, and 50–60% ing specifically and strongly bound to the SHBG [32-33]. Unbound testosterone diffuses passively through the cell membranes into the target cell, where it binds to the specific androgen receptor (AR) [34]. The serum free testosterone (FT) and the albumin-bound testosterone represent the fractions readily available for biological action.

Androgenic actions of testosterone are mediated via binding to the AR, either directly or after 5α reduction to DHT, whereas part of the physiological actions of testosterone results from its aromatization to estradiol, which binds to estrogen receptors (ERs). The AR does not bind substantially androstenedione, DHEA, or DHEAS, and it is assumed that the androgenic effects of these steroids are attributable to their transformation to testosterone in the tissues. Recently, an endothelial plasma membrane DHEA binding site has been described, which still requires, however, functional proof of receptor activity [35]. There is also evidence for DHEA interaction with the γ-aminobutyric acid receptor [36]. Testosterone can also exert rapid, nongenomic effects, in part via binding to a G protein-coupled membrane receptor for the SHBG-testosterone complex that initiates a cAMP mediated, transcription-independent signaling pathway affecting calcium channels [37-38]. Recently, Braun and Thomas [39] reported the presence of a high-affinity membrane AR in the Atlantic croaker.

Influence of Aging on Blood Concentrations Testosterone

In healthy adult males, morning levels of serum testosterone vary between around 315 and 1000 ng/dl (11 and 35 nmol/liter) [78], the blood production rate [mean concentration multiplied by metabolic clearance rate (MCR)] ranging from 4 to 10 mg/d (14 to 35 μmol/d) [40]. Plasma levels show circadian variations with amplitude of approximately 35%, highest levels in the morning and lowest levels in the late afternoon [41]. Although there are also ultradian variations in testicular

secretion of testosterone as a consequence of episodic stimulation by pulsatile pituitary secretion of LH, discrete testosterone secretory episodes are usually not clearly identified in peripheral blood [42].

As early as 1958, Hollander and Hollander [43] reported a decrease of spermatic vein testosterone concentration in elderly men and, soon afterward, Kent and Acone [44] reported an age-associated decline in blood production rate, which was subsequently confirmed by several other authors [46-47]. However, this does not necessarily translate into lower plasma levels because the MCR also decreases with aging in men. Nevertheless, in the early seventies several authors reported an age-associated decline of serum testosterone levels from the fourth or fifth decade of life on. Although this has long been controversial, this decline has now been confirmed both by a large series of cross-sectional studies [4848] and by several longitudinal studies [49-52]. In fact, the age-associated decrease appears more important in the longitudinal than in cross sectional studies, which might be explained by a bias toward healthier subjects in the former, whereas community-dwelling elderly are more likely to show deterioration than an improvement of their health status during follow-up [52].

There is an age-associated increase of SHBG levels by about 1.2% per year [52], so that the decrease of FT and bioT serum levels is larger than that of total serum testosterone [53-56].

Mechanisms of the age-associated decline in blood androgen levels. There are three different aspects to the changes in serum testosterone levels in aging men: first, there are primary testicular changes with a diminished testicular secretory capacity; second, there is an altered neuroendocrine regulation of the Leydig cells with apparent failure of the feedback mechanisms to fully compensate; and third, there is an independent increase of SHBG binding capacity [57-58].

The production of testosterone, dihydrotestosterone (DHT), and androstenedione by the human testis during advancing age was studied; it was found that in old age the testicular production of DHT decreases significantly as well as its concentration in peripheral venous plasma. Spermatic androstenedione is unchanged while testosterone is decreased in senescence. This finding suggests that the decreased Leydig cell function in old age may be partly due to an enzymatic defect in the testicular steroid genesis pathway because androstenedione is a direct precursor of testosterone [47]. Endocrine profiles change with aging independently of specific disease states. Among the major androgens and metabolites, androstane-3 alpha,17 beta-diol (androstanediol; 0.8%/yr) and androstanediol glucuronide (0.6%/yr) declined less rapidly than free testosterone, while 5 alpha-dihydrotestosterone remained essentially constant between ages 39-70 yr. Androstenedione declined at 1.3%/yr, a rate comparable to that of free testosterone, while the adrenal androgen dehydroepiandrosterone (3.1%/yr) and its sulfate (2.2%/yr) declined 2-3 times more rapidly. Serum concentrations of estrogens and cortisol did not change significantly with age [51].

Primary testicular changes: Stimulation with human chorionic gonadotropin (hCG) [50, 59-60], with pulsatile administration of GnRH or with biosynthetic LH after down regulation of endogenous LH secretion with leuprolide [61], has consistently revealed a diminished secretory capacity of the Leydig cells in the elderly compared with young men. This decrease in testicular secretory reserve appears to involve a reduction of the number of Leydig cells [62-65].

The enzymes involved in the synthesis of testosterone are decreased with aging, as is the steroidogenic acute regulatory protein, which is involved in the transport of cholesterol into mitochondria [66-68]. There is also evidence for a shift in testicular androgen biosynthesis favoring the Δ_4 over the Δ_5 steroids, analogous to the situation for the adrenals [69]. In healthy, community-dwelling men over age 75 yr, mean testicular volume is reduced by about 30% relative to that in young men [70]. Both total testosterone and estradiol showed a significant stepwise decrease with age starting in the early adult years, while estrone did not vary. These relations of testosterone and estradiol with age remained significant after adjustment for body mass index, subscapular skin fold, and tobacco and alcohol consumptions and they were not modified by exclusion of the men who reported chronic disease [56].

Factors Affecting Blood Androgen Levels in the Healthy Elderly

Healthy males show a slow and steady age-associated decline in plasma levels of testosterone and nonspecifically bound testosterone with, however, at all ages large between subject variations. Although the mechanisms of this variability have not been completely elucidated, several physiological and lifestyle-related factors appear to play a role.

a. Intrasubject variability and random effects. There have been reports of circannual variations in plasma testosterone with amplitude of up to 30% and maximum around October to December for studies performed in the Western hemisphere [71-73]. But the reports are not consistent with some studies finding no significant variation or maximum levels rather in spring or summer [72]. At present it is also not possible to differentiate between potential contributory factors such as latitude, climate, and/or diet. In any case, the large between-subject variability in serum testosterone was also seen when the study design avoided seasonal effects [74].

b. Circadian rhythmicity. Studies performing blood sampling in the morning have often shown an age-related decrease in testosterone levels, while those using afternoon samples have failed to show such a decrease. These results suggested the possibility that the circadian rhythm in serum testosterone levels might be altered with normal aging in men. Hourly blood samples were obtained for 24 h from 1 young (mean age, 52.2 yr) and 12 old (mean age, 17 yr) healthy men. Total testosterone levels were measured by RIA. The circadian rhythm in serum testosterone levels found in normal young men was markedly attenuated or absent in

healthy elderly men; the early morning rise in testosterone levels characteristic of young men was not present in old age. Mean testosterone levels for the entire 24-h day were lower in healthy old men than in young men. These results demonstrate a clear decrease in serum testosterone levels in healthy old men compared to those in young men and provide an explanation for the inability to demonstrate an age-related decline in testosterone levels in earlier studies using serum samples obtained in the afternoon [75]. Serum testosterone levels peak in early adulthood in men and fall progressively with age. Since sex hormone binding globulin increases with age, the unbound forms of testosterone (free and bioavailable testosterone) fall more steeply than total testosterone levels [76]. There is a diurnal pattern of serum testosterone level with the highest levels occurring in the early morning with greatest excursions seen in younger versus older men [75-77].

As men get older, there is a decline in many biological systems; the endocrine systems share such changes in hormone levels. There are decreases in the secretion rate of testosterone, adrenal androgen precursors (e.g. dehydroepiandrosterone (DHEA) and its sulphate ester (DHEAS)), thyroid hormones (e.g. tri-iodothyronine), growth hormone and insulin-like growth factor-I (IGF-I), renin and angiotensin. There is general consensus that serum levels of testosterone decline with ageing. This decline begins at about age 30 and decreases progressively as men get older. Cross sectional studies have shown that serum free testosterone concentration decreases more with age than the total testosterone because of an age-related increase in serum SHBG levels [78-79].

c. Ethnicity and heredity. Heredity plays an important role as shown by studies in twins by Meikle et al. [80-81], which revealed that genes determine as much as 25–76% of the total variation of plasma levels of gonadotropins, testosterone, FT, estradiol, and estrone. In these studies, only 12% of the variation in serum DHT levels was explained by heredity, but there appears to be a strong genetic influence (over 40%) in the tissue formation and the production rate of DHT. Nongenetic, familial factors may also substantially contribute to the determination of plasma hormone levels, e.g. for SHBG [82]. The genetic basis underlying the heredity of testosterone and FT is presently unknown. Considering the complexity of testosterone synthesis and the regulation of its secretion, there obviously is a broad range of candidate genes [83].

d. Fat mass and its distribution. Adiposity as assessed by the body mass index (BMI) [i.e., body weight (in kilograms)/ body height (in meters) is an important negative determinant of total serum testosterone levels, mainly via its effects on SHBG levels [84]. The latter are in turn positively associated with insulin sensitivity, as indicated by the consistent finding of a negative correlation of SHBG with insulin serum levels [54, 85-92]. Similarly, a negative association of serum SHBG and total testosterone with leptin levels was observed [93-94], this negative association being [93] or not being [94] maintained after adjustment for BMI. Overall, negative associations with serum testosterone levels tend to be most pronounced for indices of abdominal adiposity [87, 90, 94-96].

A study examined lifestyle and behavioral correlates of the change in total testosterone over 13 years in 66 men aged 41-61 years; Age, body weight, weight change, leisure time activity level, and alcohol intake were not related to the change in total testosterone. The decrease in endogenous testosterone was associated with an increase in triglycerides and a decrease in high density lipoprotein cholesterol in multivariate analysis controlling for obesity and other lifestyle covariates. . This longitudinal study confirms a gradual decline in total testosterone levels with advancing age in older men and provides evidence that lifestyle and psychosocial factors are related to this decline. Decreases in endogenous testosterone levels with age in men are associated with potentially unfavorable changes in triglycerides and high density lipoprotein cholesterol [51].

e. Diet. As far as the influence of diet is concerned, reports in the literature are rather divergent. In a study in elderly monks [53], plasma testosterone and FT levels were similar in vegetarian and non-vegetarian subjects. It has been reported [97] that Chinese in Beijing had lower serum testosterone and SHBG levels, but testosterone MCR similar to Chinese living in Pennsylvania and following a Western diet. Other data strongly suggest that fiber, lignan, and diets rich in isoflavone are associated with higher serum SHBG and total testosterone levels compared with Western diets [98-102], but FT levels may not be significantly different [100]. In 1552 men aged 40–70 yr in the MMAS, fiber intake and protein intake were significant independent positive and negative determinants, respectively, of serum SHBG, whereas neither total caloric intake, nor fat or carbohydrate consumption contributed significantly; the lack of a significant role of carbohydrate and fat intake makes it unlikely that the effects of diet would be mediated only by changes in serum insulin levels [103]. Interestingly, low protein intake is known to be associated with low serum IGF-I levels [100], which can be hypothesized to play a role in the age-related increase of serum SHBG [54, 104-105].

The role of endogenous sex hormones in many diseases makes understanding factors that influence levels of these hormones increasingly important. Analyses of age-hormone associations, adjusting for weight, body mass index, alcohol ingestion, smoking, physical activity, caffeine intake, specimen storage time, and disease status, were undertaken. Bioavailable testosterone and bioavailable estradiol levels decreased significantly with age independently of covariates. Total testosterone and estradiol levels decreased with age only when analyses were controlled for confounders. The importance of the age-associated decline in endogenous sex hormone levels, particularly levels of bioavailable testosterone and bioavailable estradiol, and their relation to disease and function in men deserve further research [106].

f. Stress. Stress evokes adaptive neuroendocrine reactions with, on the one hand, activation of the stress-responsive corticotropic, sympatho-adrenal, and soma-

totropic axes and, on the other hand, suppression of the gonadal axis through restraining of hypothalamic GnRH secretion [107-111]. One of several possible mechanisms underlying the latter inhibition of GnRH secretion may involve corticotrophin stimulated secretion of dogenous opiates [112-115]. Acute fasting for 48 or 84 h has been reported to result in a substantial reduction of serum testosterone in healthy men through reduced L Hpulse frequency and [107-108, 116], which can be reversed by pulsatile administration of GnRH [111] and may involve a specific metabolic signal rather than a nonspecific reaction to stress [117]. Interestingly, elderly men appear to be relatively resistant to the metabolic stress of fasting compared with young men [107].

For several types of acute physical stress (e.g., temperature, pain, injury, strenuous exercise) or psychological stress, it has been reported that they can inhibit gonadal function [118-123]. For these various forms of stress, there is little information on whether the elderly may be less or more susceptible. In a study of young and older athletes completing a triathlon (lasting 9–12 h in young men and 11–16 h in older men), there were no differences in observed absolute decrease in serum testosterone levels [124]. As assessed in a small group of subjects, insulin-induced hypoglycemia resulted in a significant decline of serum testosterone in healthy young men but not in elderly men, although the cortisol response was robust and even slightly greater than in the young [53]. It has also been reported that serum testosterone levels appear more affected in the acute phase after myocardial infarction in middle-aged men with a mean age of 49 yr compared with elderly men with mean age of 70 yr [53]. Overall, it does appear that in elderly men plasma testosterone levels, albeit lower than in young men, may be less susceptible to decrease in response to acute stress.

g. Other lifestyle-related factors. Serum total testosterone and SHBG are reported to increase transiently during acute physical exercise of moderate intensity [125, 126], an effect that appears to result from hemo concentration and decreased testosterone MRC [127]. At all ages in adult men, serum testosterone and FT levels are 5–15% higher in (actual) smokers compared with nonsmokers [53, 54, 128-130]. Moderate alcohol consumption has no marked effect on serum testosterone [103].

h. Exercise. Short-term exercise produces a transient elevation in serum testosterone levels in elderly men, which is partly due to an increase in serum SHBG concentrations. The concomitant increase in total protein and the rapid return of total protein and SHBG to baseline values after exercise indicate that hemoconcentration partly contributes to the exercise-associated increase in circulating testosterone levels [131].

A study conducted to determine the relationship between aging, life-style factors and health-related factors and endogenous sex hormone levels, showed the important determinants of sex hormones were age, BMI, waist circumference, smoking, general health status and physical activity. Furthermore, it can be concluded that general health status modified the effect between sex hormones and age. For future observational studies it should be taken into account that the above-mentioned determinants may alter the association between sex hormones and diseases and related conditions [132].

Androgen Metabolism

Part of the metabolism of testosterone is activating, consisting in its conversion to the bioactive metabolites DHT and estradiol. Most testosterone entering prostate tissue is bio transformed to DHT, and in most tissues, with the important exception of muscle tissue, DHT is the principal active androgen, which acts mainly locally, only a small fraction escaping into the general circulation. Blood production rates of DHT and estradiol are lower than the total quantity of these steroids actually formed in the organism, a large fraction of locally produced hormone being further metabolized in situ.

Testosterone catabolism involves 5α/5β reduction of the double bond between carbons 4 and 5, 3α/3β reduction in ring A, and 17β hydroxyl oxidation, this enzymatic degradation taking place to some extend in peripheral tissues and for a large part in the liver. DHEA is first metabolized to androstenedione, under the influence of a 3β hydroxysteroid dehydrogenase, the subsequent metabolism being identical to that of testosterone. The end metabolites of endogenous androgens, i.e., androsterone, etiocholanolone, and 5α/5β androstane-3α,17 β diol are either glucuronidated under the influence of uridine diphosphate glucuronyltranferase or sulfated under the influence of a sulfokinase, these hydrosoluble conjugates being excreted by the kidneys [133]. Androstanediol glucuronide (ADG) is considered by many as an important parameter of androgen action in women [134-135], but in males its major precursor being testosterone (70%), with 30% deriving from DHEAS [136], determination of ADG does not offer much interest. The urinary excretion of ADG decreases significantly with age [137]; the ratio of urinary 5α /5β metabolites decreases with age, a consequence of a decrease of 5α reductase type 2 activities [138].

Clinical Significance of the Age-Associated Decrease in Androgen Levels

In distinction from women, for whom the menopause signs the irreversible end of reproductive life as well as the end of cyclic ovarian activity, with as a consequence low sex hormone levels in all postmenopausal women, in men fertility persists until very old age and the age-associated decrease in testosterone levels is slowly progressive. Until the eighth decade, a substantial proportion of men still have FT and bioT levels within the normal range for young men. Subnormal testosterone levels are thus not a generalized feature of aging, and as a rule androgen deficiency is only partial. Therefore, the terms partial androgen deficiency of the aging male or late onset hypogonadism have been proposed as more appropriate than the terms andropause or male climacteric, which have the connotation of a generalized phenomenon and of permanent infertility.

Does the Decrease of Androgen Levels Translate Clinically?

Arguments indicating such clinical significance could be sought in similarities between the symptomatology of aging and that of androgen deficiency in young hypogonadal men, as well as in associations between (severity of) symptoms and androgen levels. It should, however, be realized that aging is accompanied by a decline of almost all physiological functions such as cardiac output, pulmonary ventilatory capacity (both reducing work capacity), renal clearance, or GH and melatonine secretion, which in conjunction with age associated changes in lifestyle such as retirement or relative sedentarism, may all contribute to the symptomatology of aging. The decrease in GH and IGF-I levels is associated with changes in lean body mass, bone density, and abdominal obesity, similar to the changes observed in hypogonadal states, whereas the age-associated decrease in melatonin secretion might play a role in the age-associated sleep disorders.

Similarities between Symptoms of Aging and Hypogonadism in Young Men

Frequent clinical manifestations of aging in males are decreased libido and sexual activity or impotence; decreased virility, with decreased sexual body hair and beard growth; decreased energy, work capacity and cognitive function with, as objective signs, decreased muscle mass and strength; decreased bone mineral density (BMD), with increased fracture risk; increased (abdominal) obesity; and slightly decreased hematocrit. This symptomatology in the elderly develops, however, slowly and progressively with decreased physical strength, weakness, decreased libido, and often erectile dysfunction, abdominal obesity, and difficulty with concentration.

Associations between Clinical Manifestations of Aging and Sex Steroid Status

In view of the multifactorial origin of aging symptoms, strong correlations with FT or bioT levels can hardly be expected, whereas the multiplicity of contributing factors renders meaningful multivariate regression analysis difficult. Furthermore, cross-sectional association cannot establish causality, whereas prospective observational studies are rare.

1. Senile osteoporosis. Aging in men is associated with continuous loss of bone and an exponential increase of the incidence of fractures of the hip [139-140] and the spine [141-142]. Moreover, in older men the consequences of fractures in terms of morbidity and mortality appear to be more severe than in their female counterparts [143-144].

Declining sex steroid levels in the elderly may adversely affect the preservation of skeletal integrity and indicates that aromatization of testosterone to estradiol is a major component of the regulation of bone metabolism in the elderly and in healthy men, there is a negative correlation between serum testosterone and FT with visceral fat [145], and in a study involving 61 middle-aged men and 271 elderly community-dwelling men aged 70–85 yr [27], BMI and fat mass were found to be negatively correlated to FT and IGF-I levels, the correlation of fat mass with FT persisting after correction for IGF-I and age. Multivariate analysis revealed that the negative correlation of FT with fat mass was determined primarily by abdominal fat mass. These findings are in agreement with findings by others [87, 146]. Khaw and Barrett-Connor [147] in a cohort study of 571 men aged 30–79 yr observed that low testosterone levels predict central obesity in men as estimated 12 yr later. The negative correlation of serum testosterone with abdominal fat might be related to the inhibition by testosterone of triglyceride uptake and lipoprotein-lipase activity in abdominal, but not in femoral, sub cutaneous fat [148]. Moreover, testosterone stimulates lipolysis and thus reduces fat storage in the fat cells [149]. The highly significant negative correlation between FT and (abdominal) body fat may be both a cause and a consequence of abdominal obesity in the elderly. Indeed, increased adiposity is itself partially responsible for a decrease of testosterone levels [54].

Moreover, decreased GH levels, as observed in elderly males [150-154] may also play a role in the age-associated changes in body composition, with GH substitution being possibly more effective than testosterone administration to reduce abdominal fat in elderly men [153].

2. Sexual function. Aging in men is accompanied by a decrease in libido and sexual activity, mean coital frequency decreasing from about four times a week at age 20–25 to two times a month at age 75–80 yr [155]. Nevertheless, only 15% of men over 60 yr deny any sexual activity [156].

The role of androgens in sexual function is shown by the effects of androgen withdrawal: within 3–4 wk there is a decline in sexual interest, the most clear effect being a decline in spontaneous erections during sleep nocturnal penile tumescence (NPT) [157]. However, whereas normal sexual function requires adequate testosterone levels, there is good evidence that the physiological range of testosterone levels is higher than required for normal sexual function, the critical testosterone level laying below 300 ng/dl (10.4 nmol/liter) [157-159]. Hence, it is not surprising that the correlation of libido with plasma testosterone levels is rather poor [160]. Nevertheless, Tsitouras et al.[161] reported that a group of elderly subjects with higher sexual activity had a higher mean testosterone level than the men in a low-activity group, whereas Schiavi et al. [162] reported that men with hypoactive sexual desire had lower testosterone levels than controls, and Pfeilschifter et al. [105] consider that the low androgen levels may contribute to the age-related decline in male sexuality.

In these studies there is, however, a broad overlap of serum testosterone levels between sexually less and more active elderly men. Moreover, other studies failed to find an association between testosterone levels and the perception of sexual functioning [163-164].

Frequency of erectile dysfunction increases dramatically with age. Androgens, which act centrally as well

as peripherally [165], where testosterone stimulates nitric oxide synthase in the corpora cavernosa [166], are essential for normal penile erection. Possibly in relation to the stimulatory effect of testosterone on nitric oxide synthase activity, a synergistic effect between androgens and inhibitors of 5-phosphodiesterase type 5 has been observed [167-168]. Nevertheless, testosterone deficiency is rarely a major cause of impotence in elderly males, although it might play a subsidiary role in 6–45% of cases [169], the most prevalent cause of erectile dysfunction being atherosclerotic pelvic arterial insufficiency [170]. There is good evidence that, NPT is androgen dependent [169].

3. Brain and psychological function. It is well accepted that cognition is frequently impaired in older men. While cognition has many functional domains, memory loss is the most frequent cognitive complaint of the elderly. Moderate or severe memory loss is reported in 4% of elderly adults (males and females between the ages of 60 and 65) increasing to 35% in those aged 85 and older. Androgens have been shown to enhance both memory and spacial skills in rats [171, 172]. Some epidemiological studies have found correlations between serum testosterone levels and general or spatial tion [173, 174]. While there is no doubt that testosterone has effects on brain development and performance in men, it is unclear if testosterone treatment will improve memory in older men. To help answer these questions, five placebo-controlled studies have investigated tive domains before and after testosterone treatment. The results are mixed without a clear definition as to what improvement might be anticipated with treatment [175]. In one clinical study, androgen replacement in elderly men improved spatial ability without changes in memory or verbal fluency [176]. Certainly properly powered and carefully controlled studies are needed to clarify whether benefits in cognition might be seen after testosterone treatment of older hypogonadal men.

Hypogonadal young and middle-aged men frequently complain of symptoms of depression and a decreased sense of well-being; non-placebo-controlled studies have suggested that mood is improved after testosterone treatment [177]. There is also evidence available that depressed mood is inversely related to serum ble testosterone levels [178]. Many studies have been done to assess the impact of testosterone on impaired mood. Unfortunately, the studies were often small and of short duration. While the results were mixed, the majority showed some degree of improvement in men who were already depressed or frail and depressed [179-180]. Androgen replacement therapy in ageing men improved general well being [181]. More detailed studies of androgen replacement on cognition in older testosterone-deficient men are needed, as are studies on the benefits to cognitive function in dementia associated with ageing [76].

4. Cognitive function. Recently, hormonal effects in the central nervous system have become a focus of interest, with emphasis on potential antiaging effects of hormonal replacement therapy. Indeed, aging is associated with deterioration of multiple aspects of cognitive performance. Studies in humans concerning the relationship between endogenous androgen levels and cognitive performance have produced inconsistent results, although there do exist striking sex differences in spatial abilities [182].

In healthy young men, positive relationships have been observed between endogenous plasma testosterone levels and visual-spatial orientation [183,184], but other studies have failed to find such an association [185, 187].

Patients with isolated hypogonadotropic hypogonadism show an impairment of spatial abilities [188, 189], which is improved by androgen treatment [190, 191]. As to the effects of endogenous testosterone levels on cognitive functions in elderly males, Morley et al [191] reported a significant correlation of the endogenous testosterone levels with visual and verbal memory, whereas in the Rancho Bernardo study [192], a higher bioT was significantly associated with better long-term verbal memory and score for a cognitive screening test. Yaffe et al. [193] found in a cross-sectional study in 310 community-dwelling men with a mean age of 73 yr that a higher bioT was associated with significantly better scores on three cognitive tests, i.e., the Mini-Mental State Examination, the Trail Making B test, and the Digit Symbol test. In the same study, cognitive function was also found to be associated with the CAG-repeat polymorphism of the AR gene [194]. In volunteers of the Baltimore Longitudinal Study of Aging, a higher free androgen index (FAI; ratio serum testosterone over SHBG) was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning, and with a reduced rate of longitudinal decline in visual memory [195].

Recently, it has been reported from the same study that lower values for FAI were associated with an increased incidence of Alzheimer's disease in 574 men aged 32 to 87 yr at baseline and followed for a mean duration of 19.1 yr; an increase of FAI with 10 nmol/nmol was associated with a 26% decrease of risk of Alzheimer's disease [196].

Sex steroids modify cortical function have been described. For example, estrogen replacement improves verbal memory in women, and animal studies have shown effects of estrogen on hippocampal synaptogenesis and function. Little is known about sex steroid effects on other aspects of memory, such as frontal lobe-mediated working memory. Testosterone supplementation improved working memory in older men, but a similar enhancement of working memory was not found in older women supplemented with estrogen. In men, testosterone and estrogen effects were reciprocal - with better working memory related to a higher testosterone to estrogen ratio. These results suggest that sex steroids can modulate working memory in men and can act as modulators of cognition throughout life [197].

A study on the role of sex hormones in the prevention of cognitive decline suggests that testosterone can be given to men with early cognitive impairment without significant concern about worsening aggressive or unwanted behaviors [198]. Testosterone plays a role in

the organization of behavior during development. Testosterone supplementation influenced the endogenous production of estradiol, and estradiol was found to have an inverse relationship to spatial cognitive performance. These results suggest that testosterone supplementation can modify spatial cognition in older men; however, it is likely that this occurs through testosterone's influence on estrogen [197].

It may therefore be concluded that the age-associated decrease in FT and bioT levels appears to contribute to the impaired cognitive functions of elderly men. Kalmijn et al [198] observed in a group of elderly males and females (mean age, 67.3 yr; range, 55–80 yr) a correlation between the cortisol/DHEAS ratio and cognitive impairment; the DHEAS level was inversely, but not significantly, related to cognitive impairment and decline. Berr et al. [199] found in 266 men over 65 yr of age, of whom 123 were over 75 yr at inclusion, no association between baseline DHEAS serum concentrations and incident cases of dementia during a 4-yr prospective follow-up.

Ageing is accompanied by an overall reduction in brain volume [200-202]. However there is considerable diversity in rates of decline for specific sub regions. Likewise, there are variable rates of decline across different cognitive domains, with some functions remaining relatively intact, and others showing unambiguous impairment [203-206].

According to the "frontal aging hypothesis", age-related cognitive decline is driven by deterioration of the frontal brain areas, notably the prefrontal cortex (PFC) [207, 208]. Indeed, neural declines in volume are found to be greatest in the frontal lobes and smallest in the sensory cortices [203, 209]. Functions involving the type of cognitive control mediated by prefrontal regions are particularly likely to decline with age. For example, impairments are seen in selective activation of goal levant information, episodic memory, prospective memory and working memory [210]. Conversely, autobiographical and automatic memory processes, mance on theory of mind tasks, and vocabulary and mantic knowledge are relatively stable across the adult life span, at least until the 7th or 8th decade [203].

More general age-related changes in the brain also include reductions in synapse density, grey and white matter, and cerebral blood flow [211]. In healthy older adults, white matter lesions are associated with tions in information processing speed [212, 213]. Along with rapid declines observed in PFC volume and function, moderate declines have also been found to develop gradually across the adult life span in the striatum, a region that is responsible for dopamine production [201]. These changes are accompanied by declines in dopamine concentration and dopamine and serotonin receptor availability in the frontal cortex [214-215]. Together, these age-related declines in PFC volume and in neurotransmitter systems are associated with declines in cognitive performance among aging adults [214].

Several behavioral and neuroimaging studies have provided evidence to suggest that executive processes, such as those involving behavioral self-regulation, planning, working, memory, inhibition, and strategic memory processes, are mediated by the ventrolateral and dorsolateral PFC [216-219]. There is evidence to suggest that the lateral regions of PFC show the largest age related declines of all the sub regions of the PFC [220].

Processes governing cognition and emotion appear to have different trajectories as people age [221, 204]. Older adults show impairment on strategic memory tasks tapping frontal lobe function, while their regulation of emotion and social behavior, also associated with the frontal lobes, is not compromised [204]. Researchers have recently attempted to account for the opposing trajectories in cognitive and emotional functioning by conceptualizing the frontal cortex as a collection of sub regions, each with specialized functions, as opposed to a homogenous unit [220]. Infact, as people get older, subjective emotional experience improves [221]. Amygdala appears to be crucial in rapid acquisition, stability and persistence of learned emotional responses, especially those involving fear. Sex differences in behavioral, cognitive, physiological, and pathological functions have recently been recognized [222]. In the cognitive and motor domains, men typically outperform women for spatial abilities, mathematical reasoning, and motor targeting, whereas women outperform men for verbal abilities, fine motor skills, and perceptual speed [223-224].

The neural correlates of cognitive gender differences remain unclear at this time. Sexually dimorphic structures are abundant in the human brain and sex differences have been reported in brain metabolite concentrations [225], in resting cerebral glucose metabolism [226], in resting cerebral blood flow [227] and in neural circuits recruited during performance of specific tasks [228-230]. However, the functional relevance of these sex differences remains unknown.

Although cognitive and brain sex differences are well documented, very little is known about the course of cognitive and brain sex differences across the lifespan. Indeed, the older population is the least studied group for cognitive sex differences [5], and findings are inconsistent regarding whether men and women differ in cognitive functioning and age-related cognitive decline. Some studies have indicated that the typical pattern of sex differences in verbal and spatial abilities generalizes from early adulthood to old age [231, 232], whereas other studies have claimed that sex differences do not persist into old age [233, 234]. Evidence for sex differences in the magnitude of age-related cognitive decline is also conflicting. Some studies have pointed to a greater age-related decline in men than in women [235], whereas other studies have pointed to a greater decline in women than in men [236]. Finally, other studies have not found sex differences in age-related cognitive decline [237]. Sex differences have also been reported in regard to aging of the brain, with most studies pointing to greater age-related changes in men than in women, but the findings are also inconsistent [238].

Investigating cognitive sex differences in an animal model that is relatively free from such confounds may provide important information on sex-specific patterns

of age-related cognitive change. Such information is crucial for the development of effective therapeutics against age-related cognitive decline [239].

There is solid evidence to postulate that androgenic masculinization of the brain during development [240] and activational effects of androgens in adulthood [241-242] underlie sex differences in spatial abilities. In aged men, gradual decline in testosterone levels has also been associated with poorer performance on some tests of spatial ability [194]. Although total plasma testosterone levels are similar between young and aged rhesus keys, levels of testosterone are reduced by 50% in aged males [243]. These age-related changes could account for the decline in hippoampal-dependent spatial working memory, as testosterone is necessary for the maintenance of normal spine density in nonhuman primates [244], increases the number of dendritic spines in the hippocampus in male and female rats [244], and affects regional brain perfusion in older hypogonadal men [245].

Conversely, female rhesus monkeys also undergo important endocrine changes with age. In particular, older female above the age of 25 were likely to be peri- or postmenopausal [246]. Because estrogen deficiency, after natural or surgical menopause, has been shown to affect the aspects of cognitive function both in women [247] and nonhuman primates [248], menopausal status may have affected spatial memory performance in older females.

5. Depression. Depression is less prevalent in men than in women. This had led to the hypothesis that sex hormones are involved in the etiology of at least some types of depression. Psychological and behavioral changes accompanying aging in males are lack of energy, decreased cognition, fatigue, memory impairment, and sleep disturbances. Several authors [249] reported that depressive subjects have lower testosterone levels than controls.

6. Quality of life. It is evident that aging is often associated with a decrease of quality of life. However, so far the rare available studies failed to show a relationship between FT or bioT and quality of life in elderly men as assessed with the SF-36 questionnaire [250]. Neuro-vegetative symptoms such as hot flushes may be more common in elderly men than generally suspected [251], but an association with the endogenous sex steroid levels has not been established in otherwise healthy elderly men. Intramuscular testosterone, administered at a dose of 200 mg every 2 weeks, does not affect the Health-related quality of life (HRQOL) of elderly males [252].

Overall, it can be concluded that there are limited observations of beneficial effects of testosterone treatment on cognitive function in elderly men, which warrant further investigation.

However, presently the limited information available with essentially negative findings for the longer duration studies does not allow us to claim clinical benefits on cognition of testosterone administration to elderly men.

7. Mood and quality of life. Several trials with androgen treatment included questionnaires on mood and/or depression. These studies failed to demonstrate a treatment effect on either mood [253, 254] or scores for geriatric depression scales [255, 256].

Risks of Androgen Treatment

Stimulation of androgen-sensitive tissues raises safety concerns about possible side effects of androgen treatment. These may include increased risk of prostatic carcinoma, benign prostatic hyperplasia, polycythemia, sleep apnea, gynecomastia and breast carcinoma, fluid retention, hypertension, lipid alterations, and atherosclerosis [257, 258].

a. Prostate. Of all the side effects, possible stimulation of prostatic cancer growth causes the most concern. So far, there is no evidence that testosterone initiates the development of prostatic carcinoma [259], but, because almost all prostatic carcinomas are androgen sensitive [260], it is evident that the presence of a clinical carcinoma is an absolute contraindication for androgen substitution.

b. Erythropoiesis. Androgens stimulate erythropoiesis, and in most studies hematocrit increased by 2–5% over baseline values during treatment, 6–25% of subjects developing erythrocytosis with hematocrit over 50% [261-269].

c. Cardiovascular risk. Although androgen action has traditionally been associated with increased risk of atherosclerosis and CAD, it is becoming increasingly clear that the relationship between exposure to endogenous and exogenous sex steroids and cardiovascular risk is complex and not fully clarified [253, 258, 270].

d. Sleep apnea. There have been rather anecdotal reports that androgen treatment can induce or exacerbate sleep apnea [271, 272], which might be especially the case in obese subjects, patients with COPD, and smokers. Liu et al. [253] observed that short-term administration of rather high doses of testosterone to healthy older men resulted in decrease of time slept and disruption of breathing pattern during sleep with longation of periods of hypoxemia,

e. Other adverse effects. Clinically significant fluid retention and hypertension are seldom observed with moderate doses of testosterone [270], but caution is advisable in patients with preexisting congestive heart failure, hypertension, or renal insufficiency.

Gynaecomastia is a benign complication occurring occasionally during testosterone treatment [270] as a consequence of peripheral aromatization of testosterone, which takes place mainly in fat tissue and is increased in elderly males. Clinical examination at initiation of treatment and during follow-up should include assessment of the presence of breast tissue, and adaptation of treatment regimen may be considered in case of opment of gynaecomastia. Carcinoma of the breast in males is rare and constitutes an absolute contraindication for androgen administration. Hepatotoxicity is a problem essentially limited to the oral use of alkylated testosterone derivatives. Local tenderness at the site of

IM injection of testosterone esters and skin irritation with use of preparation for transdermal administration are not uncommon, the latter being more frequent with testosterone patches than with gel [270].

The risk of side effects is greater in elderly than in young hypogonadal men. Indeed, the high frequency of BPH, subclinical prostatic carcinoma, atherosclerosis, and hypertension makes the elderly more prone than young men to many of the abovementioned adverse effects. Recently, in a comparative dose ranging study in young and older men with suppressed endogenous testosterone secretion by administration of a long-acting GnRH agonist, Bhasin et al. [273] observed a higher incidence of erythrocytosis, leg edema, and prostate events in the elderly, whereas the young had acne more frequently. Moreover, as illustrated in the latter study, identical treatment regimens can result in higher plasma levels in the elderly compared with the young, a consequence of age related decrease in MCR [46, 274, 275].

CONCLUDING REMARKS

In this review, we briefly summarized the physiological framework for changes in sex steroid hormone production in elderly men and reviewed the present state of knowledge on the extent, the modulating factors, the mechanisms, and the possible clinical consequences of such changes. We discussed the diagnosis of androgen deficiency in elderly men and reviewed the data obtained in controlled clinical trials of androgen administration and related pharmacological interventions in elderly men. It is now well established that aging in healthy men is accompanied by a progressive, albeit individually variable, decline of serum testosterone with steeper decrease of the serum fractions that are not bound to SHBG and are readily available for biological action, which is in turn accompanied by a modest decline of non-SHBG-bound serum levels of its aromatization product estradiol and is paralleled by a sharp drop in production of the adrenal androgen DHEA(S). The age-related changes in sex steroid production in healthy elderly men are of mixed testicular and neuroendocrine origin and can be accentuated by disease or its treatment. However, although many factors that can modulate androgen production in elderly men have been identified, the basis for the large inter individual variation in serum testosterone at all ages remains poorly understood and deserves to be identified as one of the major knowledge deficits in the field of andrology.

A large body of observational data has been accumulated on the question of the possible clinical consequences of the decline of sex steroid hormone production in elderly men; although most studies have limitations inherent to a cross sectional design and prospective observational studies remain scarce. It is fair to conclude that the whole of the evidence indicates that these age-related hormonal changes are likely to play at least in some men a contributory role in part of the clinical alterations that accompany aging, with some of the most convincing documentation pertaining to age-related changes in body composition and senile bone loss. It is also clear, however, that for many clinical signs and symptoms in elderly men that are reminiscent of the clinical picture in young hypogonadal men, the data remain inconclusive as to a role of age-related partial androgen deficiency.

Overall, there is presently little if any conclusive evidence for a role of "physiological" age-related decline of sex steroid production on morbidity or deterioration of quality of life in elderly men; nevertheless this does not mean that elderly men cannot suffer "pathological" hypogonadism with markedly subnormal testosterone serum levels.

A major limitation to assess the clinical impact of the changes in androgen production in the elderly is the lack of a reliable and practical marker of androgen action in the tissues and our consequent relative ignorance as to physiological androgen requirements in elderly men in general and a fortiori as to individualized androgen needs. In this context, diagnosis of hypogonadism in elderly men is difficult and in borderline cases always uncertain. In view of these diagnostic limitations and the inconclusive evidence that modest age-related androgen deficits really matter clinically, it is advisable to reserve the diagnosis of hypogonadism, with its implication of considering testosterone administration, for those elderly men with manifest hypogonadism as established by the presence of both clear clinical symptoms and serum testosterone levels frankly below the range for young men.

Given the yet-unresolved issues of the exact androgen requirements in elderly men and of the real clinical significance of the age-associated decrease of serum testosterone levels, it seems wise not to label androgen administration or related pharmacological interventions in clinical trials in the elderly as "substitutive treatment." Indeed, the latter implies that a hormonal deficit has been established, that the hormonal treatment reestablishes physiological sex steroid hormone exposure and by doing so corrects or prevents documented clinical consequences of such a deficit. Clearly, to date we lack the knowledge base to fulfill these criteria. Many of the performed trials have included substantial proportions of men with serum testosterone levels well within the normal range for young men. Finally, given the lessons from experience in the field of hormone replacement therapy in menopausal women, the not uncommon inexplicit view that clinical introduction of a substitutive treatment is acceptable with a lower level of clinical documentation than would be required for any classical pharmacological treatment should be vigorously combated in the present context. Indeed, unless the elderly men considered for treatment are frankly hypogonadal they should be considered as healthy subjects even if they have borderline low serum testosterone levels relative to those in young men, the implication being that they should not be treated with testosterone or related compounds as long as the clinical efficacy and safety has not been established with the highest level of evidence. Although some of the performed controlled clinical trials have provided interesting results on intermediary endpoints suggesting the possibility of clinical

benefits, at present there is no demonstration of benefits in terms of hard clinical outcomes. Clearly, the scale of the studies that have been performed to date would not allow for establishing clinical benefit and, even less so, long-term safety. To perform the large-scaled studies needed to establish the risk-benefit profile of androgen administration to elderly men will require a major collaborative effort of scientists, the pharmaceutical industry, and funding agencies. Meanwhile, androgen treatment should be strictly reserved for elderly men with clear hypogonadism, who deserve equal access to treatment as their younger counterparts, be it that in the elderly the criteria for diagnosis should be more conservative and the follow-up more stringent. In elderly as in young hypogonadal men, once initiated testosterone treatment will usually be lifelong. A detailed discussion of treatment modalities falls beyond the scope of this review. Evidently, in view of the higher risk for adverse events in the elderly, careful follow-up of treatment is mandatory with particular attention for erythrocytosis, prostate disease, arterial hypertension, and fluid retention.

KEY POINTS

- Ageing is associated with multiple endocrine dysfunctions.
- Testosterone deficiency is common in men over the age of 60.
- Since sex hormone binding globulin (SHBG) level increases with age, free testosterone levels fall more than total testosterone concentrations.
- Clinical signs and symptoms of hypogonadism should accompany low hormone levels before testosterone treatment is considered.
- There are multiple potential benefits for testosterone treatment of older men.
- These include increased muscle mass, strength and function, decreased body.
- Fat, improved bone mineral density, improved libido and, in some instances.
- Increased erectile function and perhaps improved cognition and mood.
- There are undefined potential risks of androgens on the prostate gland including that of symptomatic benign prostate hyperplasia (BPH) and cancer.
- Exclusion criteria for testosterone treatment in the older male population include existing prostate cancer and high red blood cell mass.
- Multiple testosterone preparations are available for the treatment of men with hypogonadism.
- It is uncertain if all of the benefits of testosterone treatment seen in younger hypogonadal men will apply to older men with equal hormone levels and this need to be investigated.
- It is unclear if testosterone treatment will enhance the risk of prostate cancer or cardiovascular disease. Long-term safety data are needed.

REFERENCES

1. Choia J, Silverman I. Processes underlying sex differences in route-learning strategies in children and adolescents. *Pers Individual Diff.* 2003;34:1153–6.
2. Silverman I, Choi J, MacKewn A, Fisher M, Moro J, Olshansky E. Evolved mechanisms underlying way finding: further studies on the hunter-gatherer theory of spatial sex differences. *Evol Hum Behav*. 2000; 21: 201–13.
3. Watson NV, Kimura D. Nontrivial sex differences in throwing and intercepting: relation to psychometrically- defined spatial functions. *Pers Individual Diff*. 1991;12:375–85.
4. Silverman I, Eals M. Sex differences in spatial abilities: evolutionary theory and data. In J. H. Barkow, L. Cosmides, & J. Tooby (Eds.), The adapted mind: evolutionary psychology and the generation of culture. New York: Oxford Press. 1992; p. 531-49
5. Kimura D. Sex and cognition. Cambridge: The MIT Press. 1999; p. 132-47.
6. Choi J, Silverman I. Sexual dimorphism in spatial behaviors: applications to route learning. *Evol Cognit*. 1996;2:165–71.
7. Williams C L, Meck WH. The organizational effects of gonadal steroids on sexually dimorphic spatial ability. *Psychoneuroendocrinology*. 1991;16:155–76.
8. Maccoby E, Jacklin C. The psychology of sex differences. Palo Alto, CA: Stanford University Press. 1974.
9. Levine SC, Huttenlocher J, Taylor A, Langrock A. Early sex differences in spatial skill. *Dev Psychol*. 1999;35:940–9.
10. Voyer D, Voyer S, Bryden, MP. Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. *Psychol Bull*. 1995;117:250–70.
11. Cherney ID, Ryalls BO. Gender-linked differences in incidental memory of children and adults. *J Exp Child Psychol*. 1999;72:305–28.
12. McGivern RF, Mutter KL, Anderson Wideman G, Bodnar M, Huston PJ. Gender differences in incidental learning and visual recognition memory: support for a sex difference in unconscious environmental awareness. *Pers Individual Diff*. 1998;25:223–32.
13. Stumpf H, Eliot J. Gender-related differences in spatial ability and the k factor of general spatial ability in a population of academically talented students. *Pers Individual Diff*. 1995;19:33–45.
14. Dabbs JM, Chang EL, Strong RA, Milun R. Spatial ability, navigation strategy, and geographic knowledge among men and women. *Evol Hum Behav*. 1998;19:89–98.
15. Galea LAM, Kimura D. Sex differences in route-learning. *Pers Individual Diff*. 1993;14:53–65.
16. Joshi MS, MacLean M, Carter W. Children's journey to school: spatial skills, knowledge and perceptions of the environment. *Br J Dev Psychol*. 1999;17:125–39.
17. Lawton CA. Gender differences in way-finding strategies: relationship to spatial ability and spatial anxiety. *Sex Roles*. 1994;30:765–79.
18. Miller LK, Santoni V. Sex differences in spatial abilities: strategic and experiential correlates. *Acta Psychologica*. 1986;62:225–35.
19. Matthews MH. The influence of gender on environmental cognition of young boys and girls. *J Genet Psychol*. 1986;147:295–302.
20. Schmitz S. Gender-related strategies in environmental development: effects of anxiety on way finding in and representation of a three-dimensional maze. *J Environ Psychol*. 1997;7:215–28.
21. McGivern RF, Huston JP, Byrd D, King T, Siegle GJ, Reilly J. Sex differences visual location memory: support for a sex-related difference in attention in adults and children. *Brain Cognit*. 1997;34:23–336.
22. Silverman I, Kastuk D, Choi J, Phillips K. Testosterone levels and spatial ability in men. *Psychoneuroendocrinology*. 1999;24:813–22.

23. Moffat SD, Hampson E, Hatzipantelis M. Navigation in a ''virtual'' maze: sex differences and correlation with psychometric measures of spatial ability in humans. *Evol Hum Behav.* 1998;19:73–87.
24. Hampson E. Sexual differentiation of spatial functions in humans. In A. Matsumoto (Ed.), Sexual differentiation of the brain. London: CRC Press. 2000; p. 279–300.
25. McGuinness D, Morley C. Sex differences in the development of visuo-spatial ability in pre-school children. *J Mental Imagery*. 1991;15:43–150.
26. Greenblatt RB. Some historic and biblical aspects of endocrinology. In: Givens JR, ed. Gynecologic endocrinology. Chicago, London: Yearbook Medical Publishers. 1976; p. 313–24.
27. Brown-Sequard CE. Effects in man of subcutaneous injections of freshly prepared liquid from guinea pig and dog testes. *CR Seances Soc Biol Ger.* 1889;9:15–419.
28. Brown-Sequard CE. Note on the effects produced on man by subcutaneous injections of a liquid obtained from the testicles of animals. *Lancet.* 1889;2:105–7.
29. Hammond GL, Ruokonen A, Kontturi M, Koskela E, Vihko R. Simultaneous radioimmunoassay of 7 steroids in human spermatic and peripheral venous-blood. *J Clin Endocrinol Metab.* 1977;45:16–24.
30. Horton R, Tait J. Androstenedione production, and conversion rates in peripheral blood and studies on the possible site of its inter conversion to testosterone. *J Clin Invest.* 1966;45:301–7.
31. Horton R, Tait J. The *in vivo* conversion of dehydroisoandrosterone to plasma androstenedione and testosterone. *J Clin Endocrinol Metab.* 1967;27:79.
32. Vermeulen A, Verdonck L. Studies on the binding of testosterone to human plasma. *Steroids.* 1968;11:609–35.
33. Dunne JF, Nisula BC, Rodbard D. Transport of steroid-hormones- binding of 21 endogenous steroids to both testosterone binding globulin and corticosteroid-binding globulin in human plasma. *J Clin Endocrinol Metab.* 1981;53:58–68.
34. Giorgi EP, Stein WD. The transport of steroids into animal cells in culture. *Endocrinology.* 1981;108:688–97.
35. Liu DM, Dillon JS. Dehydroepiandrosterone activates endothelial cell nitric-oxide synthase by a specific plasma membrane receptor coupled to G (i2,3). *J Biol Chem.* 2002;277:21379–88.
36. Baulieu EE, Robel P, Schumacher M. Neurosteroids: beginning of the story. *Int Rev Neurobiol.* 2001;46:1–32.
37. Rosner W, Hryb DJ, Khan MS, Nakhla AM, Romas NA. Sex hormone-binding globulin. Binding to cell membranes and generation of a second messenger. *J Androl.* 1992;13:101–6.
38. Benten WPM, Lieberherr M, Giese G, Wrehlke C, Stamm O, Sekeris CE, Mossmann H, Wunderlich F. Functional testosterone receptors in plasma membranes of T cells. *FASEB J.* 1999;13:123–33.
39. Braun AM, Thomas P. Biochemical characterization of a membrane androgen receptor in the ovary of the Atlantic croaker (*Micropogonias undulatus*). *Biol Reprod.* 2004;71:146–55.
40. Vermeulen A. Secretion rates of androgens in human subjects. Progress in endocrinology. *Excerpta Medica International Congress Series* 2003;863–870.
41. Resko JA, Eik-Nes KA. Diurnal testosterone levels in peripheral plasma of human male subjects. *J Clin Endocrinol Metab.* 1966;26:573–6.
42. Veldhuis JD, King JC, Urban RJ, Rogol AD, Evans WS, Kolp LA, Johnson ML. Operating characteristics of the male hypothalamo- pituitary-gonadal axis. Pulsatile release of testosterone and follicle-stimulating-hormone and their temporal coupling with luteinizing hormone. *J Clin Endocrinol Metab.* 1987;65:929–41.
43. Hollander N, Hollander VP. The microdetermination of testosterone in human spermatic vein blood. *J Clin Endocrinol Metab.* 1958;19:966–70.
44. Kent JZ, Acone AB. Plasma androgens and aging. In: Vermeulen A, Exley D, eds. Androgens in normal and pathological conditions. Amsterdam: Excerpta Medica Foundation 1966; p. 31–5.
45. Baker HWD, Burger HG, de Kretser DM, Hudson B, Endocrinology of aging: pituitary testicular axis. In: James VHT, ed. Proc 5th International Congress of Endocrinology, Amsterdam, Holland, 1977, Excerpta Medica Foundation, p. 179–183.
46. Vermeulen A, Verdonck L, Rubens R. Testosterone secretion and metabolism in male senescence. *J Clin Endocrinol Metab.* 1972;34:730–5.
47. Giusti G, Gonnelli P, Borrelli D, Fiorelli G, Forti G, Pazzagli M, Serio M. Age-related secretion of androstenedione, testosterone and dihydrotestosterone by human testis. *Exp Gerontol.* 1975;10: 241–5.
48. Vermeulen A. Androgens in the aging male. *J Clin Endocrinol Metab*. 1991;73:221–4.
49. Morley JE, Kaiser FE, Perry 3rd HM, Patrick P, Morley PMK, Stauber PM, Vellas B, Baumgartner RN, Garry PJ. Longitudinal changes in testosterone, luteinizing hormone, and folliclestimulating hormone in healthy older men. *Metabolism.* 1997;46:410–3.
50. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab.* 2001;86:724–31.
51. Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. *Am J Epidemiol.* 1997;146:609–17.
52. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB . Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab.* 2002;87:589–98.
53. Deslypere JP, Vermeulen A. Leydig-cell function in normal men. Effect of age, life-style, residence, diet, and activity. *J Clin Endocrinol Metab*. 1984;59:955–62.
54. Vermeulen A, Kaufman JM, Giagulli VA. Influence of some sex hormone-binding globulin and androgen levels in aging or obese males. *J Clin Endocrinol Metab.* 1996;81:1821–6.
55. Ferrini RL, Barrett-Connor E. Sex hormones and age: a cross sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. *Am J Epidemiol.* 1998;147:750–4.
56. Simon D, Preziosi P, Barrettconnor E, Roger M, Saintpaul M, Nahoul K, Papoz L. The influence of aging on plasma sex hormones in men. The Telecom-study. *Am J Epidemiol.* 1992;135:783–91.
57. Kaufman JM, Vermeulen A. Declining gonadal function in elderly men. *Baillieres Clin Endocrinol Metab*. 1997;11:289–309.
58. Kaufman JM, T'Sjoen G, Vermeulen A. 2004 Androgens in male senescence. In: Nieschlag E, Behre HM, eds. Testosterone, action, deficiency, substitution. 3rd ed. Cambridge, UK: Cambridge University Press; 497–541.
59. Nankin HR, Lin T, Murono EP, Osterman J. The aging Leydig cell. 3. Gonadotropin stimulation in men. *J Androl.* 1981;2:181–9.
60. Mulligan T, Iranmanesh A, Kerzner R, Demers LW, Veldhuis JD. Two-week pulsatile gonadotropin releasing hormone infusion unmasks dual (hypothalamic and Leydig cell) defects in the healthy aging male gonadotropic axis. *Eur J Endocrinol.* 1999;141:257–66.
61. Mulligan T, Iranmanesh A, Veldhuis JD. Pulsatile iv infusion of recombinant human LH in leuprolide-suppressed men unmasks impoverished Leydig-cell secretory responsiveness to midphysiological LH drive in the aging male. *J Clin Endocrinol Metab.* 2001;140:5547–53.
62. Sniffen RC. The testes. I. The normal testis. *Arch Pathol (Chic).* 1950;50:259–84.

63. Harbitz TB. Morphometric studies of Leydig cells in elderly men with special reference to histology of prostate. An analysis in an autopsy series. *Acta Pathol Microbiol Scand*. [A] 1973;81:301–14.
64. Neaves WB, Johnson L, Porter JC, Parker CR, Petty CS. Leydig cell numbers, daily sperm production, and serum gonadotropin-levels in aging men. *J Clin Endocrinol Metab.* 1984;59:756–63.
65. Neaves WB, Johnson L, Petty CS. Age-related change in numbers of other interstitial cells in testes of adult men. Evidence bearing on the fate of Leydig cells lost with increasing age. *Biol Reprod.* 1985;33:259–69.
66. Zirkin BR, Chen HL. Regulation of Leydig cell steroidogenic function during aging. *Biol Reprod.* 2000;63:977–81.
67. Luo L, Chen H, Zirkin BR. Leydig cell aging: steroidogenic acute regulatory protein (StAR) and cholesterol side chain cleavage enzyme. *J Androl.* 2001;22:149–56.
68. Culty M, Luo LD, Yao ZX, Chen HL, Papadopoulos V, Zirkin BR. Cholesterol transport, peripheral benzodiazepine receptor, and steroidogenesis in aging Leydig cells. *J Androl.* 2002;23:439–47.
69. Vermeulen A, Deslypere JP. Intratesticular unconjugated steroids in elderly men. *J Steroid Biochem Mol Biol*. 1986;24:1079–83.
70. Mahmoud AM, Goemaere S, El-Garem Y, Van Pottelbergh I, Comhaire FH, Kaufman JM. Testicular volume in relation to hormonal indices of gonadal function in community-dwelling elderly men. *J Clin Endocrinol Metab.* 2003;88:179–84.
71. Smals AGH, Kloppenborg PWC, Benraad TJ. Circannual cycle in plasma testosterone levels in man. *J Clin Endocrinol Metab*. 1976;42:979–82.
72. Svartberg J, Jorde R, Sundsfjord J, Bonaa KH, Barrett-Connor E. Seasonal variation of testosterone and waist to hip ratio in men: the Tromso study. *J Clin Endocrinol Metab*. 2003;88:3099–104.
73. Dabbs Jr JM. Age and seasonal variation in serum testosterone concentration among men. *Chronobiol Int.* 1990;7:245–9.
74. Kaufman JM, T'Sjoen G, Vermeulen A 2004 Androgens in male senescence. In: Nieschlag E, Behre HM, eds. Testosterone, action, deficiency, substitution. 3rd ed. Cambridge, UK: Cambridge University Press; p. 497–541.
75. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab.* 1983;56:1278–81.
76. Ronald S. Swerdloff. Androgens and the ageing male. Best Practice & Research Clinical Endocrinology & Metabolism. Vol. 18, No. 3, 2004; p. 349–62.
77. Tenover JS, Matsumoto AM, Clifton D & Bremner WJ. Age-related alterations in the circadian rhythms of pulsatile luteinizing hormone and testosterone secretion in healthy men. *J Gerontol.* 1988;43: M163–9
78. Vermeulen A. Androgen replacement therapy in the aging male. A critical evaluation. *J Clin Endocrinol Metab*. 2001;86:2380–90.
79. Snyder PJ. Effects of age on testicular function and consequences of testosterone treatment. *J Clin Endocrinol Metab*. 2001;86:2369–72.
80. Meikle AW, Bishop DT, Stringham JD, West DW. Quantitating genetic and nongenetic factors that determine plasma sex steroid variation in normal-male twins. *Metabolism.* 1986;35:1090–5.
81. Meikle AW, Stringham JD, Bishop DT, West DW. Quantitating genetic and nongenetic factors influencing androgen production and clearance rates in men. *J Clin Endocrinol Metab*. 1988;67:104–9.
82. Handelsman DJ. Estimating familial and genetic contributions to variability in human testicular function: a pilot twin study. *Int J Androl.*1997;20:215–21.
83. Ukkola O, Rankinen T, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C. A genome-wide linkage scan for steroids and SHBG levels in black and white families: the HERITAGE Family Study. *J Clin Endocrinol Metab*. 2002;87:3708–20.
84. Demoor P, Goossens JV. An inverse correlation between body weight and the activity of the steroid binding globulin in human plasma. *Steroidologia.* 1970;1:129–36.
85. Giagulli VA, Kaufman JM, Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. *J Clin Endocrinol Metab.* 1994;79:997–1000.
86. Haffner SM, Valdez RA, Stern MP, Katz MS. Obesity, body fat distribution and sex hormones in men. *Int J Obes.* 1993;17:643–9.
87. Vermeulen A, Goemaere S, Kaufman JM. Sex hormones, body composition and aging. *Aging Male.* 2003;.2:8–16.
88. Heald AH, Ivison F, Anderson SG, Cruickshank K, Laing I, Gibson JM. Significant ethnic variation in total and free testosterone concentration. *Clin Endocrinol* (Oxf) 2003;58:262–6.
89. Zumoff B, Strain GW, Miller LK, Rosner W, Senie R, Seres DS, Rosenfeld RS. 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*. 1990;71:929–31.
90. Khaw KT, Barrett-Connor E. Low endogenous androgens predict central obesity in men. *Ann Epidemiol.* 1992;2:675–82.
91. Plymate SR, Matej LA, Jones RE, Friedl KE. Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep-G2) cell-line by insulin and prolactin. *J Clin Endocrinol Metab.* 1988;67:460–4.
92. Simon D, Preziosi P, Barrett-Connor E, Roger M, Saint-Paul M, Nahoul K, Papoz L. Interrelation between plasma testosterone and plasma insulin in healthy adult men: the Telecom Study. *Diabetologia.* 1992;35:173–7.
93. Van den Saffele JK, Goemaere S, De Bacquer D, Kaufman JM. Serum leptin levels in healthy ageing men: are decreased serum testosterone and increased adiposity in elderly men the consequence of leptin deficiency? *Clin Endocrinol* (Oxf). 1999;51:81–8.
94. Haffner SM, Miettinen H, Karhapaa P, Mykkanen L, Laakso M. Leptin concentrations, sex hormones, and cortisol in nondiabetic men. *J Clin Endocrinol Metab*. 1997;82:1807–9.
95. Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Despres JP, Bouchard C. Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: The HERITAGE family study. *J Clin Endocrinol Metab*. 2000;85:1026–31.
96. Chang TC, Tung CC, Hsiao YL. Hormonal changes in elderly men with non-insulin-dependent diabetes-mellitus and the hormonal relationships to abdominal adiposity. *Gerontology.* 1994;40:260– 7.
97. Santner SJ, Albertson B, Zhang GY, Zhang GH, Santulli M, Wang C, Demers LM, Shackleton C, Santen RJ. Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. *J Clin Endocrinol Metab*. 1998;83:2104–9.
98. Reed MJ, Cheng RW, Simmonds M, Richmond W, James VHT. Dietary lipids: an additional regulator of plasma levels of sex hormone binding globulin. *J Clin Endocrinol Metab*. 1987;64:1083–5.
99. Belanger A, Locong A, Noel C, Cusan L, Dupont A, Prevost J, Caron S, Sevigny J. Influence of diet on plasma steroid and sex plasma-binding globulin levels in adult men. *J Steroid Biochem Mol Biol*. 1989;32:829–33.
100. Key TJA, Roe L, Thorogood M, Moore JW, Clark GMG, Wang DY. Testosterone, sex hormone-binding globulin, calculated free testosterone, and estradiol in male vegans and omnivores. *Brit J Nutr.* 1990;64:111–9.
101. Adlercreutz H. Western diet and Western diseases: some hormonal and biochemical mechanisms and associations. *Scand J Clin Lab Invest.* 1990;201:3–23.
102. Hamalainen EK, Adlercreutz H, Puska P, Pietinen P. Decrease of serum total and free testosterone during a low-fat high fiber-diet. *J Steroid Biochem Mol Biol*. 1983;18:369–70.

103. Longcope C, Feldman HA, McKinlay JB, Araujo AB. Diet and sex hormone-binding globulin. *J Clin Endocrinol Metab*. 2000;85:293–6.
104. Erfurth EMT, Hagmar LE, Saaf M, Hall K. Serum levels of insulin-like growth factor I and insulin-like growth factor-binding protein 1 correlate with serum free testosterone and sex hormone binding globulin levels in healthy young and middle-aged men. *Clin Endocrinol* (Oxf). 1996;44:659–64.
105. Pfeilschifter J, Scheidt-Nave C, Leidig-Bruckner G, Woitge HW, Blum WF, Wuster C, Haack D, Ziegler R. Relationship between circulating insulin-like growth factor components and sex hormones in a population-based sample of 50- to 80-year-old men and women. *J Clin Endocrinol Metab*. 1996;81:2534–40.
106. Ferrini RL, Barrett-Connor E. Sex hormones and age: a cross sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. *Am J Epidemiol*. 1998;147:750–4.
107. Bergendahl M, Veldhuis JD. Altered pulsatile gonadotropin signaling in nutritional deficiency in the aging male. *Trends Endocrinol Metab*. 1995;61:145–59.
108. Bergendahl M, Vance ML, Iranmanesh A, Thorner MO, Veldhuis JD. Fasting as a metabolic stress paradigm selectively amplifies cortisol secretory burst mass and delays the time of maximal nyctohemeral cortisol concentrations in healthy men. *J Clin Endocrinol Metab*. 1996;81:692–9.
109. Bergendahl M, Aloi JA, Iranmanesh A, Mulligan TM, Veldhuis JD. Fasting suppresses pulsatile luteinizing hormone (LH) secretion and enhances orderliness of LH release in young but not older men. *J Clin Endocrinol Metab*. 1998;83:1967–75.
110. Hartman ML, Veldhuis JD, Johnson ML, Lee MM, Alberti KG, Samojlik E, Thorner MO. Augmented growth hormone (GH) secretory burst frequency and amplitude mediate enhanced GH secretion during a two-day fast in normal men. *J Clin Endocrinol Metab.* 1992;74:757–65.
111. Aloi JA, Bergendahl M, Iranmanesh A, Veldhuis JD. Pulsatile intravenous gonadotropin-releasing hormone administration averts fasting-induced hypogonadotropism and hypoandrogenemia in healthy, normal weight men. *J Clin Endocrinol Metab*. 1997;82:1543–8.
112. Gambacciani M, Yen SSC, Rasmussen DD. GnRH release from the mediobasal hypothalamus—in vitro regulation by oxytocin. *Neuroendocrinology.* 1986;42:181–3.
113. Olster DH, FerinM. Corticotropin-releasing hormone inhibits gonadotropin-secretion in the ovariectomized rhesus monkey. *J Clin Endocrinol Metab.* 1987;65:262–7.
114. Petraglia F, Vale W, Rivier C. Opioids act centrally to modulate stress-induced decrease in luteinizing hormone in the rat. *Endocrinology.* 1986;119:2445–50.
115. Xiao E, Luckhaus J, Niemann W, FerinM. Acute inhibition of gonadotropin secretion by corticotropin-releasing hormone in the primate: are the adrenal glands involved. *Endocrinology.* 1989;124:1632–7.
116. Cameron JL, Weltzin TE, Mcconaha C, Helmreich DL, Kaye WH. Slowing of pulsatile luteinizing hormone secretion in men after 48 hours of fasting. *J Clin Endocrinol Metab.* 1991;73:35–41.
117. Knobil E. Inhibition of luteinizing hormone secretion by fasting and exercise: "stress" or specific metabolic signals? *Endocrinology.* 1993;132:1879–80.
118. Christiansen K, Knussmann R, Couwenbergs C. Sex hormones and stress in the human male. *Horm Behav*. 1985;19:426–40
119. Francis KT. The relationship between high and low trait psychological stress and serum indicators of stress. *Experientia.* 1981;37:1086–7.
120. Hellhammer DH, Hubert W, Schurmeyer T. Changes in saliva testosterone after psychological stimulation in men. *Psychoneuroendocrinology.* 1985;10:77–81.
121. Nilsson PM, Moller L, Solstad K. Adverse effects of psychosocial stress on gonadal function and insulin levels in middle-aged males. *J Int Med.* 1995;237:479–86.
122. Opstad PK. Androgenic hormones during prolonged physical stress, sleep, and energy deficiency. *J Clin Endocrinol Metab.* 1992;74:1176–9.
123. Kujala UM, Alen M, Huhtaniemi IT. Gonadotrophin-releasing hormone and human chorionic gonadotrophin tests reveal that both hypothalamic and testicular endocrine functions are suppressed during acute prolonged physical exercise. *Clin Endocrinol* (Oxf). 1990;33:219–25.
124. Malarkey WB, Hall JC, Rice Jr RR, O'Toole ML, Douglas PS, Demers LM, Glaser R. The influence of age on endocrine responses to ultraendurance stress. *J Gerontol.* 1993;48:M134–9.
125. Zmuda JM, Thompson PD, Winters SJ. Exercise increases serum testosterone and sex hormone binding globulin levels in older men. *Metabolism.* 1996;45:935–9.
126. Kraemer WJ, Hakkinen K, Newton RU, Nindl BC, Volek JS, McCormick M, Gotshalk LA, Gordon SE, Fleck SJ, Campbell WW, Putukian M, Evans WJ. Effects of heavy resistance training on hormonal response patterns in younger vs. older men. *J Appl Physiol.* 1999;87:982–92.
127. Cadoux-Hudson TA, Few JD, Imms FJ. The effect of exercise on the production and clearance of testosterone in well trained young men. *Eur J Appl Physiol Occup Physiol*. 1985;54:321–5.
128. Dai WS, Gutai JP, Kuller LH, Cauley JA. Cigarette-smoking and serum sex hormones in men. *Am J Epidemiol*. 1988:128:796–805.
129. Barrett-Connor E, Khaw KT. Cigarette smoking and serum sex hormones in men. *Am J Epidemiol.* 1987;128:796–805.
130. Field AE, Colditz GA, Willett WC, Longcope C, McKinlay JB. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. *J Clin Endocrinol Metab.* 1994;79:1310–6.
131. Zmuda JM, Thompson PD, Winters SJ. Exercise increases serum testosterone and sex hormone binding globulin levels in older men. *Metabolism.* 1996;45:935–9.
132. Muller M, den Tonkelaar I, Thijssen JHH, Grobbee DE, van der Schouw YT. Endogenous sex hormones in men aged 40–80 years. *Eur J Endocrinol.* 2003;149:583–9
133. Griffin JE, Wilson JD 1980 The testis. In: Bondy PK, Rosenberg LE, eds. Metabolic control and disease. Philadelphia: W. B. Saunders; p. 1535–8.
134. Horton R, Hawks D, Lobo R. Androstanediol glucuronide in plasma. A marker of androgen action in idiopathic hirsutism. *J Clin Invest.* 1982;69:1203–6.
135. Paulson RJ, Serafini PC, Catalino JA, Lobo RA. Measurements of 3_,17_-androstanediol glucuronide in serum and urine and the correlation with skin 5-reductase activity. *Fertil Steril.* 1986;46:222–6.
136. Deslypere JP, Sayed A, Punjabi U, Verdonck L, Vermeulen A. Plasma 5-androstane-3,17-diol and urinary 5-androstane- 3,17-diol glucuronide, parameters of peripheral androgen action: a comparative study. *J Clin Endocrinol Metab*. 1982;54:386–91
137. Vermeulen A, Giagulli VA. Physiopathology of plasma androstanediol- glucuronide. *J Steroid Biochem Mol Biol.* 1991;39:829–33.
138. Kuttenn F, Mowszowicz I, Schaison G, Mauvais-Jarvis P. Androgen production and skin metabolism in hirsutism. *J Endocrinol.* 1977;75:83–91.
139. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA. Lifetime risk of hip fractures is underestimated. *Osteoporos Int.* 1998;8:599–603.
140. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a worldwide projection. *Osteoporos Int.* 1992;2:285–9.
141. Felsenberg D, Silman AJ, Lunt M, Armbrecht G, Ismail AA, Finn JD, Cockerill WC, Banzer D, Benevolenskaya LI, Bhalla A, Bruges AJ, Cannata JB, Cooper C, Dequeker J, Eastell R, Felsch B, Gowin W, Havelka S, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopes VA, Lorenc R, Lyritis G, Masaryk P, Matthis C, Miazgowski T, Parisi G, Poor G, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan JJ, Todd

CJ, Weber K, Woolf AD, Yershova OB, Reeve J, O'Neill TW. Incidence of vertebral fracture in Europe: results from the European Prospective Osteoporosis Study (EPOS). *J Bone Miner Res.* 2002;17:716–24.

142. Van der Klift M, De Laet CEDH, McCloskey EV, Hofman A, Pols HAP. The incidence of vertebral fractures in men and women: the Rotterdam Study. *J Bone Miner Res*. 2002;17:1051–6.
143. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet.* 1999;353:878–82.
144. Poor G, Atkinson EJ, Lewallen DG, O'Fallon WM, Melton LJ. Age-related hip fractures in men: clinical spectrum and short-term outcomes. *Osteoporos Int.* 1995;5:419–26
145. Seidell JC, Bjorntorp P, Sjostrom L, Kvist H, Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. *Metabolism.* 1990;39:897–901.
146. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab.* 2000;85:3276–82.
147. Khaw KT, Barrett-Connor E. Low endogenous androgens predict central obesity in men. *Ann Epidemiol.* 1992;2:675–82.
148. Marin P, Oden B, Bjorntorp P. Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens. *J Clin Endocrinol Metab.* 1995;80:239–43.
149. Tenover JS. Androgen administration to aging men. *Endocrinol Metab Clin North Am.* 1994;23:877–92.
150. Vermeulen A. Nyctohemeral growth hormone profiles in young and aged men: correlation with somatomedin-C levels. *J Clin Endocrinol Metab*. 1987;64:884–8.
151. Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half life of endogenous GH in healthy men. *J Clin Endocrinol Metab.* 1991;73:1081–8.
152. Jorgensen JO, Vahl N, Hansen TB, Thuesen L, Hagen C, Christiansen JS. Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition. *Clin Endocrinol* (Oxf). 1996;45:681–8.
153. Munzer T, Harman SM, Hees P, Shapiro E, Christmas C, Bellantoni MF, Stevens TE, O'Connor KG, Pabst KM, St Clair C, Sorkin JD, Blackman MR. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. *J Clin Endocrinol Metab*. 2001;86:3604–10.
154. Tzankoff SP, Norris AH. Effect of muscle mass decrease on age-related BMR changes. *J Appl Physiol.* 1977;43:1001–6.
155. Tsitouras PD, Bulat T. The aging male reproductive system. *Endocrinol Metab Clin North Am*. 1995;24:297–315.
156. Verwoerdt A, Pfeiffer E, Wangh AS. Sexual behavior in senescence. *Geriatrics.* 1969;24:137–54.
157. Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual-behavior in normal young men. *J Clin Endocrinol Metab*. 1994;78:711–6.
158. Gooren LJ. Androgen levels and sex functions in testosterone treated hypogonadal men. *Arch Sex Behav*. 1987;16:463–73.
159. Buena F, Swerdloff RS, Steiner BS, Lutchmansingh P, Peterson MA, Pandian MR, Galmarini M, Bhasin S. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil Steril.* 1993;59:1118–23.
160. Schiavi R 1996 Androgens and sexual function in men. In: Oddens B, Vermeulen A, eds. Androgens and the aging male. London: Parthenon Publishing Group; p. 111–28.
161. Tsitouras PD, Martin CE, Harman SM. Relationship of serum testosterone to sexual activity in healthy elderly men. *J Gerontol.* 1982;37:288–93.
162. Schiavi RC, Schreiner-Engel P, White D, Mandeli J. Pituitary gonadal function during sleep in men with hypoactive sexual desire and in normal controls. *Psychosom Med*. 1988;50:304–18.
163. Perry PJ, Lund BC, Arndt S, Holman T, Bever-Stille KA, Paulsen J, Demers LM. Bioavailable testosterone as a correlate of cognition, psychological status, quality of life, and sexual function in aging males: implications for testosterone replacement therapy. *Ann Clin Psychiatry*. 2001;13:75–80.
164. T'Sjoen G, Goemaere S, De Meyere M, Kaufman JM. Perception of males' aging symptoms, health and well-being in elderly community-dwelling men is not related to circulating androgen levels. *Psychoneuroendocrinology*. 2004;29:201–14.
165. Mills TM, Reilly CM, Lewis RW. Androgens and penile erection: a review. *J Androl*. 1996;17:633–8.
166. Lugg JA, Rajfer J, Gonzalez-Cadavid NF. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide mediated penile erection in the rat. *Endocrinology*. 1995;136:1495–501.
167. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol* (Oxf). 2003;58:632–8.
168. Shab singh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol*. 2004;172:658–63.
169. Morley JE. Impotence. *Am J Med.* 1986;80:897–905.
170. Sullivan ME, Keoghane SR, Miller MA. Vascular risk factors and erectile dysfunction. BJU Int. 2001;87:838–45.
171. Alexander GM. Androgens and cognitive function. In Bhasin S, Gabelnick HL, Spieler JM, Swerdloff RS, Wang C & Kelly C (eds) Pharmacology, Biology, and Clinical Applications of Androgens: Current Status and Future Prospects. New York: Wiley–Liss, 1996; p. 169–77.
172. Frye CA, Seliga AM. Testosterone increases analgesia, anxiolysis, and cognitive performance of male rats. *Cognitive, Affective and Behavioral Neuroscience*. 2001;1:371–81.
173. Christiansen K 1998 Behavioural correlates of testosterone. In: Nieschlag E, Behre HM, eds. Testosterone, action, deficiency, substitution. 2nd ed. New York: Springer; p. 107–42.
174. McKeever WF, Deyo RA. Testosterone, dihydrotestosterone and spatial task performances of males. *B Psychonomic Soc*. 1990;28: 305–8.
175. Cherrier MM, Anawalt BD, Herbst KL, et al. Cognitive effects of short-term manipulation of serum sex steroids in healthy young men. *J Clin Endocrinol Metab.* 2002;87:3090–6.
176. Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. *Behav Neurosci*. 1994;108:325–32.
177. Wang C, Alexander G, German N, et al. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. *J Clin Endocrinol Metab*. 1996;81:3578–83
178. Barett-Connor E, Kritz Silverstein D. Gender differences in cognitive function with age: The Rancho Bernardo study. *J American Geriatrics Soc* 1999;47:159-64.
179. Pope Jr HG, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized placebo-controlled trial. *American J Psychiatry*. 2003;160: 105–11.
180. Rabkin JG, Wagner GJ, Rabkin R. Testosterone therapy for human immunodeficiency virus-positive men with and without hypogonadism. *J Clin Psychopharmacol*. 1999;19:19–27
181. Morley JE, Perry HM, Kaiser FE, et al. Effect of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J American Geriatric Soc*. 1993;41:149–52.

182. Kimura D. Sex, sexual orientation and sex hormones influence human cognitive function. *Curr Opin Neurobiol*. 1996;6:259–63.
183. Gordon HW, Lee PA. A relationship between gonadotropins and visuospatial function. *Neuropsychologia*. 1986;24:563–76.
184. McKeever WF, Deyo RA. Testosterone, dihydrotestosterone and spatial task performances of males. *B Psychonomic Soc*. 1990;28: 305–8.
185. Kampen DL, Sherwin BB. Estradiol is related to visual memory in healthy young men. *Behav Neurosci*. 1996;110:613–7.
186. McKeever WF, Rich DA, Deyo RA, Connor RI. Androgens and spatial ability: failure to find a relationship between testosterone and ability measures. *B Psychonomic Soc*. 1987;25:440.
187. Hier DB, Crowley Jr WF. Spatial ability in androgen-deficient men. *N Engl J Med*. 1982;306:1202–5.
188. Buchsbaum MS, Henkin RI. Perceptual abnormalities in patients with chromatin negative gonadal dysgenesis and hypogonadotropic hypogonadism. *Int J Neurosci*. 1980;11:201–9.
189. Cherrier MM, Craft S, Bremner WJ. Cognitive effects of exogenous testosterone administration in eugonadal and hypogonadal men. *Int J Neuropsychol Soc*. 1988;4:16–20.
190. Morley JE, Kaiser F, Raum WJ, Perry III HM, Flood JF, Jensen J, Silver AJ, Roberts E. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. *Proc Natl Acad Sci USA*. 1997;94:7537–42.
191. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. *J Clin Endocrinol Metab*. 1999;84:3681–5.
192. Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. *J Am Geriatr Soc*. 2002;50:707–12.
193. Yaffe K, Edwards ER, Lui LY, Zmuda JM, Ferrell RE, Cauley JA. Androgen receptor CAG repeat polymorphism is associated with cognitive function in older men. *Biol Psychiatry*. 2003;54:943–6.
194. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab*. 2002;87:5001–7.
195. Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. *Neurology*. 2004;62:188–93.
196. Janowsky JS, Chavez B, Orwoll E. Sex steroids modify working memory. *J Cogn Neurosci*. 2000;12:407–14.
197. Kenny AM, Fabregas G, Song CW, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci*. 2004;59:75–8.
198. Kalmijn S, Launer LJ, Stolk RP, de Jong FH, Pols HA, Hofman A, Breteler MM, Lamberts SW. A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *J Clin Endocrinol Metab*. 1998;83:3487–92.
199. Berr C, Lafont S, Debuire B, Dartigues JF, Baulieu EE. Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community-based study. *Proc Natl Acad Sci USA*. 1996;93:13410–5.
200. Morrison JH, Hof PR. Life and death ofneurons in the aging brain. *Science*. 1997;278:412-9.
201. Raz N. Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In FIM Craik and TA Salthouse (Eds.) The hand book of aging and cognition 2000 (2nd ed.,) Mahwah, NJ: Erlbaum, p. 1-90.
202. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *J Neuroscience*. 2003;23:3295-301.
203. Hedden, T, Gabrieli, JDE. Insights into the ageing mind: A view from cognitive neuroscience. *Neuroscience*. 2004;5:87-96.
204. Mather M. Aging and emotional memory. In D. Reisberg and Hertel P (Eds.), Memory and emotion 2004, Oxford: University press, p. 272-307.
205. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. *Psychol Aging*. 2002;17: 299-320.
206. Prull MW, Gabrielli JDE, Bunge SA. Age-related changes in memory: A cognitive neuroscience perspective. In FIM Craik and TA Salthouse (Eds.) The hand book of aging and cognition 2000 (2nd ed.,) Mahwah, NJ: Erlbaum, p. 91-153.
207. Greenwood, PM. The frontal ageing hypothesis evaluated. *J of International Neuropsychol Soc*. 2000;6:705-26.
208. West RL. An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull*. 1996;120:272-92.
209. Tisserand DJ, Jolles J. On the involvement of prefrontal networks in cognitive ageing. *Cortex*. 2003;39:1107-28.
210. Hasher, L, Zacks, RT, May, CP. Inhibitory control, circadian arousal, and age. In D. Gopher & Koriat A. (Eds.), Attention and performance XVII. Cognitive regulation of performance; Interaction of theory and application. Cambridge MA: MIT Press. 1999; p. 653-75.
211. Jernigan, TL, Archibald, SL, Fennema-Notestine, C, Gamst, AC, Stout, JC, Bonner, J. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging*. 2001;22:581-94.
212. De Carli, C, Murphy, DG, Tranh, M, Grady, CL, Haxby, JV, Gillette, JA. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. 1995;45:2077-84.
213. De Groot, JC, De Leeuw, FE, Oudkerk, M, Van Gun, J, Hofman, A, Jolles, J. Cerebral white matter lesions and cognitive function; The Rotterdam scan study. *Annals Neuro*. 2000;47:145-51.
214. Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, Hitzemann R, Smith G, Logan J. Association between decline in brain dopamine activity with age and cognitive and motor impairment in health individuals. *American J Psychiatry*. 1998;155:344-9.
215. Wang GJ, Volkow ND, Logon J, Fowler JS, Schyler D, MacGregor RR, Hitzemann RJ, Gjedde A, Wolf AP. Evluation of age-related changes in serotonin 5-HT2 and dopamine D2 receptor availability in health human subjects. *Life Sciences*. 1995;56:249-53.
216. Kane, MJ, Engle, RW. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bull Rev*. 2002;9:637-71.
217. Rypma B, Berger JS, D'Esposito M. The influence of working-memory demand and subject performance on prefrontal cortical activity. *J Cognitive Neuroscience*. 2002;14:721-31.
218. Bunge, SA, Ochsner, KN, Desmond JE, Glover GH, Gabrieli JD. Prefrontal regions involved in keeping information in and out of mind. *Brain*. 2001;124:2074-86.
219. Wagner AD, Maril A, Bjork RA, Schacter DL. Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *Neuroimage*. 2001;14:1337-74.
220. Tisserand DJ, Pruessner JC, Arigita EJS, Van Boxtel MPJ, Evans AC, Jolles J, Uylings HBM. Regional frontal cortical volumes decrease differentially in aging: An MRI study to compare volumetric approaches and voxel-based morphometry. *Neuroimage*. 2002;17:657-69.
221. Cartensen, LL, Isaacowitz, DM and Charles, ST. Taking time seriously: A theory of socio-emotional selectivity. *American Psychologist*. 1999;54:165-81.
222. Wizemann TM, Pardue Ml (Eds.). Committee on understanding the biology of sex and gender differences 2001: Vol. 10. Exploring the biological contributions to human health: Does sex matter? Washington, DC: National Academy Press.
223. Halpern DF. Sex differences in cognitive abilities (3rd ed.). Mahwah, NJ: Lawrence Erlbaum Associates.

224. Hampson E. Sex differences in human brain and cognition: The influence of sex steroids in early and adult life. In JB Becker, SM Breedlove, D Crews, MM McCarthy (Eds.) Behavioral endocrinology 2002 (2nd Edn.,) Cambridge, MA, MIT Press, p. 579-628.

225. Grachev ID, Apkarian Av. Chemical heterogenecity of the living human brain: A proton MR spectroscopy study on the effects of sex, age and brain region. *Neuroimage*. 2000;11:554-63.

226. Gur RC, Mozley LH, Mozley PD, Resnick SM, Karp JS, Alavi A. Sex differences in regional cerebral glucose metabolism during a resting state. *Science.* 1995;267:528-31.

227. Esposito G, Van Horn JD, Weinberger Dr, Berman KF. Gender differences I cerebral blood flow as function of cognitive state with PET. *J Nuclear Medicine.* 1996;37:559-64.

228. Groh G, Wunderlich AP, Spitzer m, Tomczak R, Reipe MW. Brain activation during human navigation: Gender different neural networks as substrate of performance. *Nature Neuroscience.* 2000;3:404-8.

229. Jordan K, Wustenberg T, Heinze HJ, Peters M, Jancke L. Women and men exhibit different cortical activation patterns during mental rotation tasks. *Neuropsycholgia*. 2002;40:2397-408.

230. Shaymitz BA, Shaywitz SE, Pugh KR, Constable RT, Skudlarski P, Fulbright RK. Sex differences in the functional organization of the brain for language. *Nature*. 1995;373:607-9.

231. Herlitz A, Nilsson LG, Backman L. Gender differences in episodic memory. *Memory and cognition* 1997;25:801-11.

232. Larrabee GJ, Crook TH. Do men show more rapid age-associated decline in simulated everyday verbal memory than do women? *Psychology Aging.* 1993;8:68-71.

233. Dollinger SM. Mental rotation performance: Age, sex and visual field differences. *Developmental Neuropsychology*. 1995;11:215-22.

234. Schwartz DW, Karp SA. Field dependence in a geriatric population. *Perceptual Motor Skills.* 1967;24:495-504.

235. Barrett-Connor E, von Muhlen DG & Kritz-Silverstein D. Bioavailable testosterone and depressive mood in older men. The Rancho-Bernardo Study. *J Clinical Endocrinol Metab.* 1999;84: 573–7.

236. Meinz EJ, Salthouse TA. Is age kinder to females than to males? *Psychonomic Bull Rev.* 1998;5:56-70.

237. Singer T, Verhaeghen P, Ghisletta P, Lindenberger U, Baltes PB. The rate of cogntion in very old age: Six year longitudinal findings in the Berlin Aging study (BASE). *Psychol Aging.* 2003;18:318-31.

238. Coffey CE, Lucke JF, Saxton JA, Ratcliff G, Unitas LJ, Billig. Sex differences in brain aging: A quantitative magnetic resonance imaging study. *Arch Neurol.* 1998;55:169-79.

239. Agnes L, Charles B, Douglas LR, Ronald JK, Mark BM, Tara LM, Lakshmi C, James GH. Sex, age and training modulate spatial memory I the rhesus monkey (Macaca mulatta). *Behavioral Neuroscience.* 2005;119(1):118-26.

240. Hines M, Fane Ba, Pasterski VL, Mathews GA, Conway GS, Brook C. Spatial abilities following prenatal androgen abnormality: Targeting and mental rotations performance in individuals with cognitive adrenal hyperplasia. *Psychoneuroendocrinology.* 2003;28:1010-26.

241. Aleman, A, Bronk E, Kessels RPC, Koppeschaar HPF, Van Honk J. A single administration of testosterone improves visuospatial ability in young women. *Psychoneuroendocrinology.* 2004;29:612-7.

242. Hooven CK, Chabris CF, Ellison PT, Kosslyin SM. The relationship of male testosterone to components of mental rotation. *Neuropscyhologia.* 2004;42:782-90.

243. Chambers KC, Hess DL, Phoenix CH. Relationship of free and bound testosterone to sexual behavior in old rhesus males. *Physiol Behav.* 1981;27:615-20.

244. Leranth C, Prange Kiel J, Frick KM, Horvath TL. Low CA1 spine synapse density is further reduced by castration I male non-human primates. *Cerebral Cortex.* 2004;14:503-10.

245. Azad N, Pitale S, Barnes WE, Friedman N. Testosterone treatment enhances regional brain perfusion in hypogonadal men. *J Clin Endocrinol Metab.* 2003;88:3064-8.

246. Gilardi KV, Shideler SE, Valverde CR, Roberts JA, Lasley BL. Characterization of the onset of menopause in the rhesus macaque. *Biology Reproduction.* 1997;57:335-40.

247. Sherwin BB. Estrogen and cognitive functioning in women. *Endocrine Reviews.* 2003;24:133-51.

248. Lacreuse A, Herndon JG, Moss MB. Cognitive function in aged ovariectomized female rhesus monkeys. *Behavioral Neuroscience.* 2000,114:506-13.

249. Knobil E. Inhibition of luteinizing hormone secretion by fasting and exercise: "stress" or specific metabolic signals? *Endocrinology.* 1993;132:1879–80.

250. Schweiger U, Deuschle M, Weber B, Korner A, Lammers CH, Schmider J, Gotthardt U, Heuser I. Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. *Psychosom Med.* 1999;61:292–6.

251. Dunbar N, Gruman C, Reisine S, Kenny AM. Comparison of two health status measures and their associations with testosterone levels in older men. *Aging Male.* 2001;4:1–7

252. Spetz ACE, Fredriksson MG, Hammar ML. Hot flushes in a male population aged 55, 65, and 75 years, living in the community of Linkoping, Sweden. *Menopause.* 2003;10: 81–7.

253. Reddy P, White CM, Dunn AB, Moyna NM, Thompson PD. The effect of testosterone on health-related quality of life in elderly males - a pilot study. *J Clin Pharm Ther.* 2000;25(6):421-6.

254. Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, Handelsman DJ. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *J Clin Endocrinol Metab.* 2003;88:3605–13.

255. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double-blind study. *J Clin Endocrinol Metab.* 2002;87:1467–72.

256. Sih R, Morley JE, Kaiser FE, Perry HM, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab.* 1997;82:1661–7.

257. Kenny AM, Fabregas G, Song CW, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol Biol Sci Med Sci.* 2004;59:75–8

258. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc.* 2003;51:101–15.

259. Rhoden EL, Morgentaler A. Medical progress: risks of testosterone replacement therapy and recommendations for monitoring. *N Engl J Med.* 2004;350:482–92.

260. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res.* 1988;48:3515–7.

261. Goldenberg SL, Bruchovsky N, Gleave ME, Sullivan LD, Akakura K. Intermittent androgen suppression in the treatment of prostate-cancer- A preliminary report. *Urology.* 1995;45:839–44.

262. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab.* 1992;75:1092–8.

263. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab.* 1997;82:3793–6.

264. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab.* 2004;89:503–10.

265. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG, Strom BL. Effect of testosterone treatment on bone min-

eral density in men over 65 years of age. *J Clin Endocrinol Metab*. 1999;84:1966–72.

266. Ly LP, Jimenez M, Zhuang TN, Celermajer DS, Conway AJ, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. *J Clin Endocrinol Metab*. 2001;86:4078–88.
267. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low normal gonadal status. *J Gerontol A Biol Sci Med Sci.* 2003;58:618–25.
268. Clague JE, Wu FCW, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl*. 1999;22:261–5.
269. Amory JK, Chansky HA, Chansky KL, Camuso MR, Hoey CT, Anawalt BD, Matsumoto AM, Bremner WJ. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. *J Am Geriatr Soc.* 2002;50:1698–701.
270. Drinka PJ, Jochen AL, Cuisinier M, Bloom R, Rudman I, Rudman D. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. *J Am Geriatr Soc.* 1995;43:899–901.
271. Wu FC, Von Eckardstein A. Androgens and coronary artery disease. *Endocr Rev* 2003. 24:183–217.
272. Matsumoto AM, Sandblom RE, Lee KA, Giblin EC, Schoene RB, Pierson DJ, Bremner WJ. Obstructive sleep-apnea induced by testosterone administration. *J Androl.* 1983;4:32-8.
273. Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Giblin EC, Pierson DJ, Bremner WJ. Testosterone replacement in hypogonadal men: effects on obstructive sleep-apnea, respiratory drives, and sleep. *Clin Endocrinol* (Oxf). 1985;22:713–21.
274. Bhasin S, Singh AB, Mac RP, Carter B, Lee MI, Cunningham GR. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *J Androl.* 2003;24:299–311.
275. Wang C, Catlin DH, Starcevic B, Leung A, DiStefano E, Lucas G, Hull L, Swerdloff RS. Testosterone metabolic clearance and production rates determined by stable isotope dilution/tandem mass spectrometry in normal men: influence of ethnicity and age. *J Clin Endocrinol Metab.* 2004;89:2936–41.

CURRENT AUTHOR ADDRESSES

Hanumanthachar Joshi, Set's College of Pharmacy, S.R. Nagar, Dharwad-580002, Karnataka, India.

Milind Parle, Division of Pharmacology, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India. Email: amanjoshi17@yahoo.com (Corresponding author)