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The Decline of Androgen Levels in Elderly Men and Its Clinical and Therapeutic Implications

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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. Albeit the clinical picture of aging in men is reminiscent of that of hypogonadism in young men and decreased testosterone production appears to play a role in part of these clinical changes in at least some elderly men, the clinical relevancy of the age-related decline in sex steroid levels in men has not been unequivocally established. In fact, minimal androgen requirements for elderly men remain poorly defined and are likely to vary between individuals. Consequently, borderline androgen deficiency cannot be reliably diagnosed in the elderly, and strict differentiation between "substitutive" and "pharmacological" androgen administration is not possible. To date, only a few hundred elderly men have received androgen therapy in the setting of a randomized, controlled study, and many of these men were not androgen deficient. Most consistent effects of treatment have been on body composition, but to date there is no evidence-based documentation of clinical benefits of androgen administration to elderly men with normal or moderately low serum testosterone in terms of diminished morbidity or of improved survival or quality of life. Until the long-term risk-benefit ratio for androgen administration to elderly is established in adequately powered trials of longer duration, androgen administration to elderly men should be reserved for the minority of elderly men who have both clear clinical symptoms of hypogonadism and frankly low serum testosterone levels. (*Endocrine Reviews* 26: 833–876, 2005)

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Abbreviations: ADG, Androstanediol glucuronide; AR, androgen receptor; bioT, bioavailable testosterone; BMD, bone mineral density; BMI, body mass index; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DEXA, dual-energy x-ray absorptiometry; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DHT, dihydrotestosterone; ECG, electrocardiogram; ER, estrogen receptor; FAI, free androgen index; FT, free testosterone; hCG, human chorionic gonadotropin; HDL-C, high-density lipoprotein-associated cholesterol; IGFBP, IGF binding protein; IMT, intima media thickness; LDL-C, low-density lipoprotein-associated cholesterol; MCR, metabolic clearance rate; MMAS, Massachussets Male Aging Study; MRI, magnetic resonance imaging; NPT, nocturnal penile tumescence; PSA, prostate-specific antigen.

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I. Introduction

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 (1). Brown-Sequard (2, 3) 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 (watery) extracts of guinea pig and dog testes' effects, which he reported in 1889 before the Societé de Biologie de Paris. Although the watery extract that Brown-Sequard used could hardly have contained any androgens, these experiments gave the impetus to research concerning testicular substances affecting sexual function, leading ultimately to the

isolation by David *et al.* (4) in 1935 of the major testicular androgen, testosterone.

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, and as such they contribute to the determination of muscle mass and strength and to that of bone and fat mass, while they indirectly also influence insulin sensitivity. 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.

II. Sex Steroids in Elderly Men

A. 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 5α-reduction of testosterone in peripheral tissues (5). 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 (6, 7); 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% being specifically and strongly bound to the SHBG (8, 9). Unbound testosterone diffuses passively through the cell membranes into the target cell, where it binds to the specific androgen receptor (AR) (10). The serum free testosterone (FT) and the albumin-bound testosterone represent the fractions readily available for biological action. Indeed, albumin-bound testosterone dissociates during tissue transit, whereas the strong binding of testosterone to SHBG will usually not allow for substantial dissociation during the tissue transit time (11). The non-SHBG-bound testosterone, *i.e.*, the combined free and albumin-bound testosterone, is often referred to as the "bioavailable testosterone" (bioT). However, the fraction actually available for biological action may vary according to the considered tissue and pathophysiological condition, and at present a reliable clinical or biochemical marker of androgen activity at the level of the tissues is still lacking.

The clinical significance of plasma DHT is very limited because most DHT formed in peripheral tissue acts locally (12), only a limited fraction escaping to the circulation where DHT is strongly bound to SHBG, only 0.8% being free. Androstenedione and DHEA are loosely bound to albumin, the binding to SHBG being negligible; DHEAS on the other hand is relatively strongly bound to albumin (13).

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 (14). There is also evidence for DHEA interaction with the γ-aminobutyric acid receptor (15).

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 (16–18). Recently, Braun and Thomas (19) reported the presence of a high-affinity membrane AR in the Atlantic croaker.

B. Influence of aging on blood concentrations

1. Testosterone. In healthy adult males, morning levels of serum testosterone vary between around 315 and 1000 ng/dl (11 and 35 nmol/liter) (20), the blood production rate [mean concentration multiplied by metabolic clearance rate (MCR)] ranging from 4 to 10 mg/d (14 to 35 μmol/d) (21). Plasma levels show circadian variations with amplitude of approximately 35%, highest levels in the morning and lowest levels in the late afternoon (22). 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 (23).

As early as 1958, Hollander and Hollander (24) reported a decrease of spermatic vein testosterone concentration in elderly men and, soon afterward, Kent and Acone (25) reported an age-associated decline in blood production rate, which was subsequently confirmed by several other authors (26–28). However, this does not necessarily translate into lower plasma levels because the MCR also decreases with aging in men (27). 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 (for review, see Ref. 29) and by several longitudinal studies (30–33) (Fig. 1). 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 a deterioration than an improvement of their health status during follow-up (33).

There is an age-associated increase of SHBG levels by about 1.2% per year (33), so that the decrease of FT and bioT serum levels is larger than that of total serum testosterone (Figs. 2 and 3) (33–37). Moreover, in the elderly the amplitude

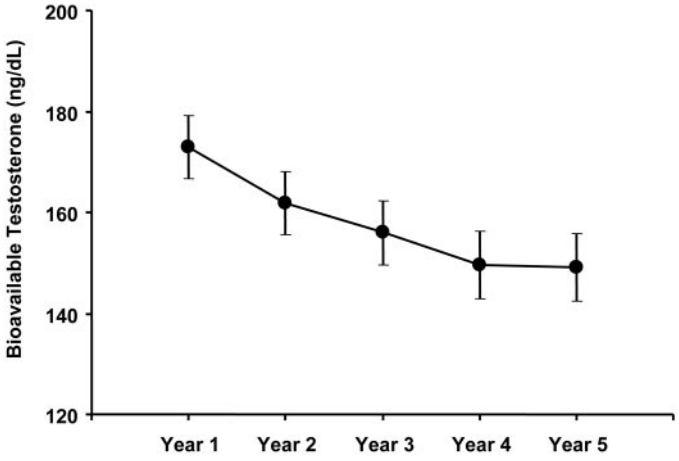

FIG. 1. Longitudinal evolution of the morning bioT (to convert to nanomoles per liter, multiply by 0.0347) in a population-based cohort of 214 ambulatory men aged 75 ± 4.0 yr at baseline and followed for a mean of 3.4 (median, 4) yr. Longitudinal changes were studied according to mixed effects modeling using SAS software (SAS Institute, Inc., Cary, NC) with additional adjustments for baseline age and BMI. Shown are yearly averages and 95% confidence interval. A highly significant systematic linear decrease was seen ($P < 0.0001$) (J. Kaufman, S. Goemaere, and D. De Bacquer, unpublished results). See Ref. 290 for details on study cohort and hormone assays.

of the circadian variation of serum testosterone, FT, and bioT is reduced (34, 38–40).

Most recent studies (31–35) in ambulatory men in whom sampling was performed in the morning show that at age 75 yr mean total serum testosterone level is about two thirds of the levels at age 25, whereas the mean FT and bioT serum levels are only about half of those in young men (Figs. 2 and 3). Nevertheless, there is at all ages an important between-subject variability of serum FT or bioT levels (Fig. 4). In the age group above 60 yr, about 20% have serum testosterone levels in the upper normal range for young men, whereas over 20% have testosterone levels below the range for young males and an even larger proportion have levels below this limit when considering FT or bioT (41) (Fig. 5). In the Baltimore Longitudinal Study of Aging (31), 19, 28, and 49% of men over ages 60, 70, and 81 yr, respectively, had total testosterone levels below the young reference range, whereas 34, 68, and 91% had subnormal levels when the FT index (FTI: T/SHBG) was used. However, the latter index is not a valid measure of FT in males, and reference values for young males may not be applicable to the elderly (42, 43).

2. Other androgens. The concentration of DHT in plasma varies between 23 and 73 ng/dl (0.8 and 2.5 nmol/liter). Only 15 to 20% is secreted by the testes, and 80% originates from conversion of testosterone by 5α-reductase type 2 in the peripheral target tissues, whereas DHT that is formed in the liver under influence of 5α-reductase type 1 is not released into the general circulation but is immediately glucuronoconjugated (44, 45); 5α-reductase activity can be differentially regulated in different target tissues (46). Cross-sectional studies do not show substantial changes in serum levels of DHT in aging men, although due to the increase in SHBG there may be a modest decrease of the free fraction (35, 47). Nevertheless, there have also been reports of decreases (48, 49) as well as increases of serum DHT with age (33).

Plasma androstenedione levels vary between 60 and 230 ng/liter (2 and 8 nmol/liter) in adult males aged 20–30 yr and significantly decline with age (50) (Fig. 2); the levels show a circadian rhythm, with maximal concentrations in the morning (51). The androgenic activity of androstenedione is dependent upon biotransformation to testosterone (blood conversion rate around 15%) (6); its MCR is about 2000 liters/d (52), and its blood production rate lies around 1.5 to 2 mg/d.

Plasma DHEA and DHEAS are secreted almost exclusively by the adrenals. Only about 10% of DHEA is derived from the gonads, whereas about 50 to 70% derives from desulfatation of DHEAS in peripheral tissues (53).

DHEA metabolism is very rapid, with a MCR around 2000 liters/d (7). Serum levels are highly age-dependent, with mean levels of about 430 ng/dl (15 nmol/liter) at age 20 yr, decreasing to 140 ng/dl (5 nmol/liter) at age 75 yr (35, 54–56) (Fig. 2). The age-associated decline of serum DHEA contrasts with maintained or even increased serum cortisol concentrations during aging. The serum levels are subject to a circadian rhythm with highest values in the morning; the daily production rate amounts to 2 to 7 mg. The blood conversion rate to testosterone is about 0.6%, and hence, its contribution to plasma testosterone levels is negligible in adult men. However, because this conversion occurs in peripheral tissues where testosterone may act locally, the conversion rate does not reflect the contribution of DHEA to androgenic activity in the tissues.

DHEAS is by far the most abundant androgen in plasma. Its mean concentration in young males is about 220 μg/dl (6 μmol/liter), *i.e.*, 10 to 20 times the concentration of cortisol, decreasing however rapidly with age (35, 54–56) (Fig. 2). Its metabolism is slow (MCR around 15 liters/d), and the blood production rate in young males lies as high as 25 to 30 mg/d (57). Due to its slow metabolism, plasma DHEAS levels do not show circadian variations. Its hormonal and metabolic effects are probably essentially attributable to its transformation to testosterone and estrogens in the tissues (58). The hormonal effects resulting from local biotransformation to these active sex steroids can presently not be quantified, but the contribution to the global androgenic and anabolic effects in men is probably modest. Indeed, it can be noted that glucocorticoid-substituted adrenal insufficiency in adult men does not result in clinically manifest hypoandrogenism, whereas conversely anorchid men have no substantial residual virilization.

3. Estrogens. There is a rapidly growing body of evidence that a number of physiological actions of testosterone in men are mediated by the ERs after its biotransformation by the aromatase cytochrome P450 enzyme in the tissues (59). Documented estrogen-mediated actions of testosterone in men include a role in the feedback regulation of LH (60, 61), a role in the regulation of skeletal homeostasis (62, 63), as well as a role in lipid metabolism and cardiovascular physiology (64, 65); among other possible estrogen actions in men, there are indications for a role in the brain (66) and in spermatogenesis (67). These estrogenic actions in men can be exerted by blood-

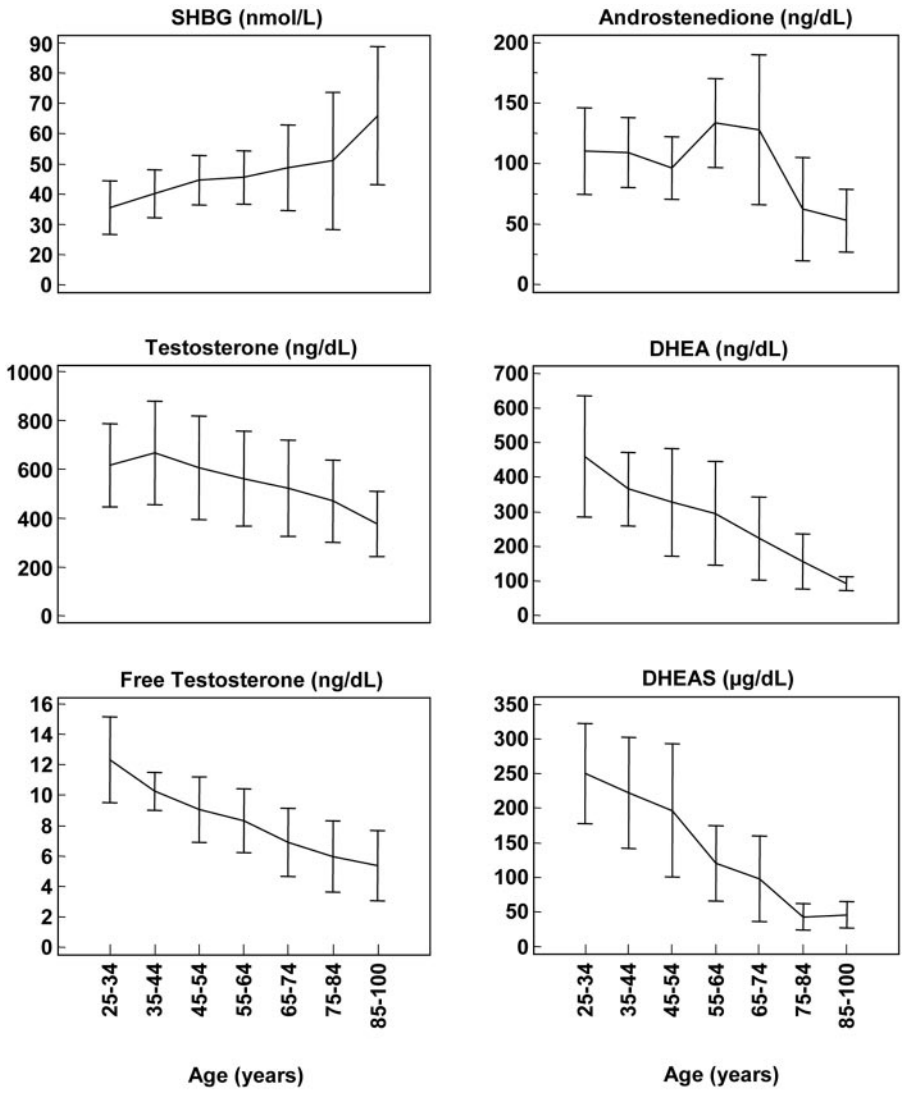

FIG. 2. Influence of age on serum androgen levels. Shown are means ± SD, according to data in Ref. 35. To convert testosterone to nanomoles per liter, multiply by 0.0347; to convert FT to picomoles per liter, multiply by 34.67; to convert androstenedione to nanomoles per liter, multiply by 0.0349; to convert DHEA to nanomoles per liter, multiply by 0.0346; and to convert DHEAS to micromoles per liter, multiply by 0.0272.

borne estrogens as well as through local aromatization of testosterone in, or in close vicinity of, the target cell. The expression of the CYP19 gene encoding the aromatase enzyme can be differentially regulated according to the tissue (68, 69).

The conversion rate of testosterone to estradiol is around 0.2%. Up to 80% of plasma estradiol originates from aromatization of testosterone and androstenedione, mainly in (sc) fat and striated muscle, although aromatase activity is present in many other tissues, including bone and the brain; no more than 20% of estradiol in the circulation is secreted by the testes. Estradiol serum concentration in the adult male is around 20 to 30 pg/ml (70 to 110 pmol/liter), with a production rate of around 45 μg/d. Plasma estradiol is also bound to SHBG but with only half the affinity of testosterone. Total plasma estradiol levels in adult men do not vary significantly with age; indeed the decrease in precursor levels (*i.e.*, testosterone and androstenedione) is compensated by an increase of fat mass and tissue aromatase activity with age (36, 70, 71). As a consequence of the age-associated increase in SHBG binding capacity, the serum concentrations of free estradiol and non-SHBG-bound or "bioavailable" estradiol do show a moderate age-associated decrease (36, 71, 72) (Fig. 3). It can be pointed out that estrogen serum levels in elderly males are higher than those in postmenopausal women (63).

C. 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 (for review, see Refs. 41 and 73).

1. Primary testicular changes. Stimulation with human chorionic gonadotropin (hCG) (74–78), with pulsatile administration of GnRH (79), or with biosynthetic LH after down-regulation of endogenous LH secretion with leuprolide (80)

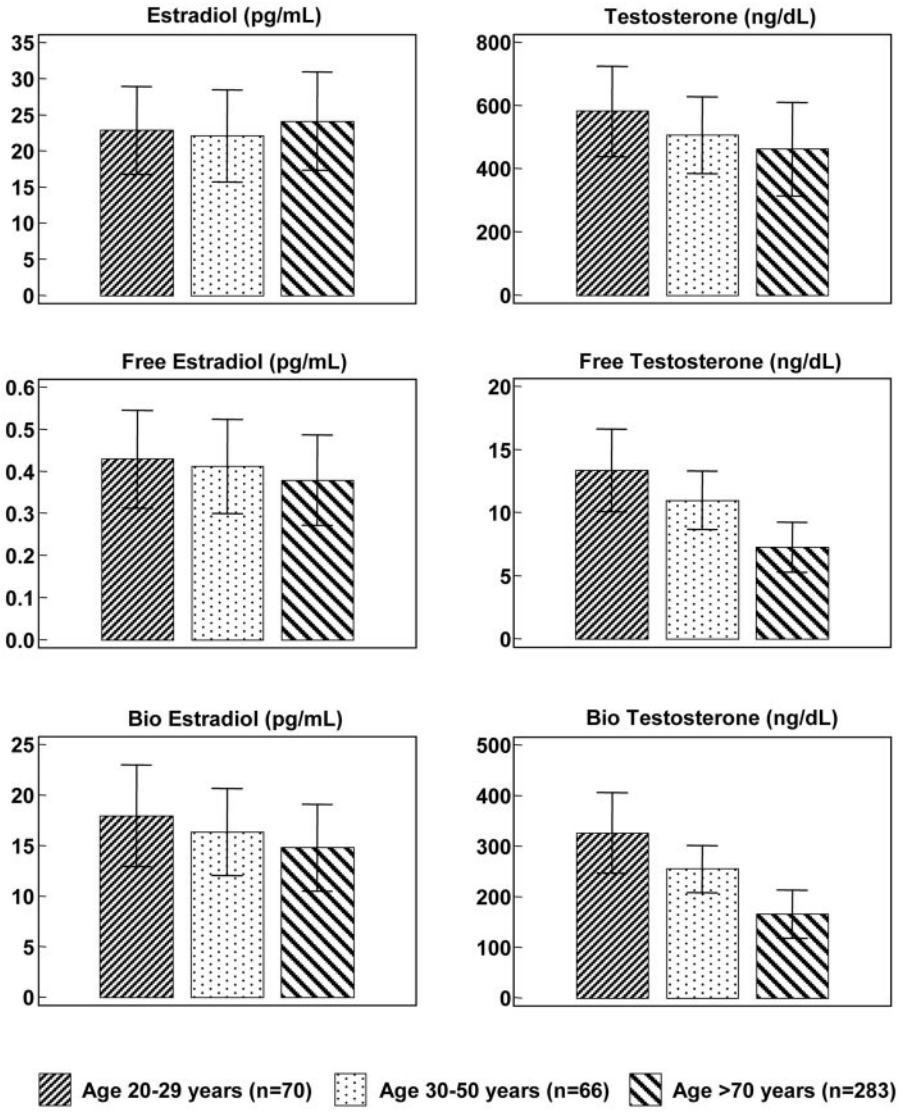

FIG. 3. Serum testosterone and estradiol fractions in young, middle-aged, and elderly community-dwelling men, according to data in Ref. 292. To convert testosterone or bioT to nanomoles per liter, multiply by 0.0347; FT to picomoles per liter, multiply by 34.67; and estradiol, free estradiol, or bioavailable estradiol to picomoles per liter, multiply by 3.676.

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 (81–84).

In old rats at least, all 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 (85–87). 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 (88). In healthy, community-dwelling men over age 75 yr, mean testicular volume is reduced by about 30% relative to that in young men (89).

2. Altered neuroendocrine regulation of Leydig cell function. Consistent with a primary testicular cause of decreased testosterone production, mean serum LH levels in the male population tend to increase with age (for review, see Refs. 29 and 90), but this increase is of modest amplitude and is inconsistent (30). Many elderly men with a serum testosterone concentration below the range for young men do not have elevated LH levels. Moreover, the modest increases in basal serum LH in elderly men appear to result in part from a slower plasma clearance rather than from increased pituitary secretion (91, 92).

Aging in men is thus also accompanied by manifest alterations in the regulation of LH secretion, the regulation of FSH secretion being better maintained (89, 93). This is conceptually of significance. Indeed, albeit the testicular secretory reserve is diminished in the elderly, there is a residual secretory capacity that should allow many elderly men to substantially raise their serum testosterone levels, provided there is an adequate LH drive.

Assessment of the secretory capacity of the pituitary gonadotropes by *in vivo* challenge with small "near physiological" doses of synthetic GnRH has revealed a maintained (79) or, in accordance with a state of relative hypoandrogenism, even a slightly increased LH response as measured by either immunoassay or bioassay in the elderly compared with young men (91). Given that the pituitary secretory capacity is preserved in the elderly, the apparent failure of the feed-

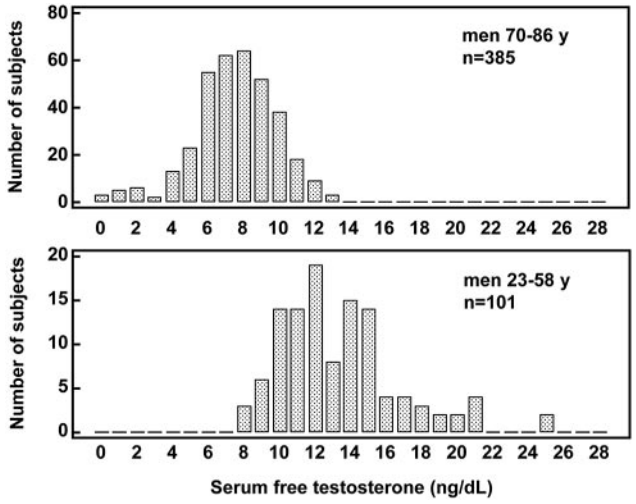

FIG. 4. Histogram for the distribution of serum FT in community-dwelling elderly men without major health problems and in a younger control population of healthy adult men. To convert FT to picomoles per liter, multiply by 34.67. [Adapted from Ref. 73 with permission from Cambridge University Press.]

back regulatory mechanisms to produce an adequate rise of serum LH must result from changes at the hypothalamic level.

The pulsatile secretion of LH, governed by episodic release of hypothalamic GnRH into the pituitary portal circulation, has in the elderly an increased irregularity compared with young men (94) with essentially unchanged (95–97) or slightly increased (98) LH pulse frequency, but with a diminished frequency of large amplitude LH pulses and a reduced mean LH pulse amplitude, which is a parameter of the stimulating effect on the Leydig cells (95, 98). By inference, it can be assumed that the diminished amplitude of LH pulses in the elderly reflects a reduced size of the GnRH bolus intermittently released into the pituitary portal circulation, which might in turn be the consequence of a reduced number of functional hypothalamic GnRH neurones, of a less efficient intermittent recruitment and/or synchronization of these neurones and/or of a down-regulation of their activity by local or systemic factors. As to the latter, an important observation is that elderly men have an increased responsiveness to the negative feedback effects of androgens (95, 96, 99, 100) (Fig. 6). It has been shown that this is not the consequence of an increased hypothalamic opioid tone (101, 102), whereas the existence of a relative leptin deficiency has also been excluded as a possible cause of the hypothalamic changes in the regulation of LH secretion in the elderly (103). The exact mechanisms underlying the decrease in hypothalamic GnRH secretion in elderly men is yet to be fully elucidated.

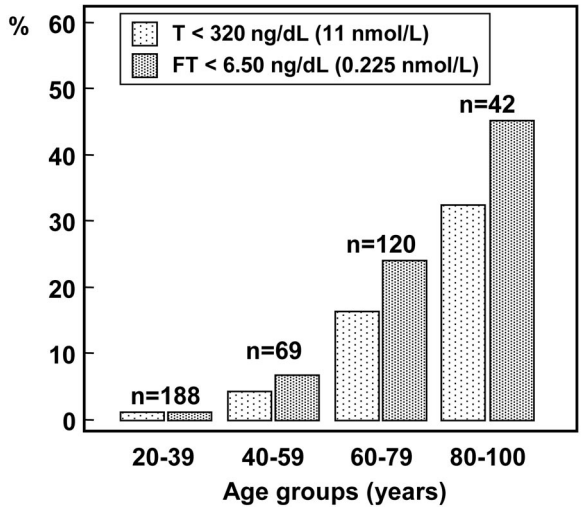

FIG. 5. Proportion of healthy men with serum testosterone (T) and FT below the laboratory reference range for young men, according to data in Refs. 20 and 35. [Adapted from Ref. 41 with permission from Elsevier.]

3. Increase of plasma SHBG binding capacity. The observation that in aging men, the decline of the serum levels of FT and bioT is accentuated relative to that of total serum testosterone as a consequence of an age-associated increase of serum SHBG might seem an unexpected finding. Indeed, in young men such an increase of serum binding capacity will be adjusted for through the testosterone feedback regulation with increase of total serum testosterone and maintained FT, as is seen for instance during thyrotoxicosis in young adult men (104). In the healthy elderly, however, the increase in plasma testosterone binding capacity is accompanied by a decrease of the nonspecifically bound fractions of testosterone, because it occurs on the background of the aforementioned testicular and neuroendocrine alterations.

The substantial age-related increase of SHBG (about 1.2%/yr) is remarkable because it occurs in the face of an increase of fat mass and insulin levels, which are strong negative determinants of SHBG levels (35, 105–108). It seems unlikely that the decreased plasma testosterone or the associated decrease of the plasma testosterone over estradiol ratio would *per se* be the cause, because the increase of SHBG seems to begin at a younger age (35). Presently, the mechanisms responsible for the age-associated increase of serum SHBG are yet to be uncovered. Involvement of the age-related decline in the activity of the somatotropic axis is an attractive, but yet to be validated working hypothesis presently supported only

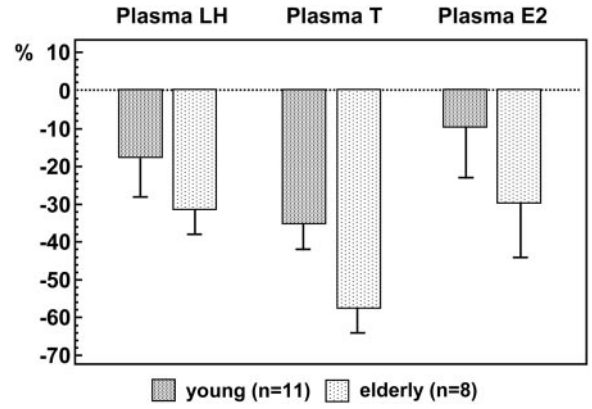

FIG. 6. Suppressing effect on serum levels of LH, testosterone (T), and estradiol (E2) in young and elderly men of transdermal administration of DHT (125 mg/d for 10 d); $P < 0.05$ for difference in percentage suppression of LH and testosterone between young and elderly men, according to data from Ref. 95.

by indirect evidence, such as the existence of a negative association between serum levels of SHBG and IGF-I and the normalization of elevated serum SHBG levels in adults with GH deficiency or GH resistance during administration of substitutive doses of GH or IGF-I, respectively (35, 109, 110).

4. Mechanisms of decreased adrenal androgen secretion. The androgen-selective decrease in plasma levels of adrenal steroids with maintained or even increased serum cortisol levels in aging men is not gender-specific, although there may be some sexual dimorphism in the observed patterns of age-related decline (111). The changes seem to be the consequence of a selective decrease in functional zona reticularis cells (112). It has been observed that after acute stimulation with ACTH, the serum DHEA response is manifestly diminished in the elderly, whereas the cortisol response is similar to that in young men (113, 114). During 3-d stimulation with 40 U of depot ACTH twice daily, increase of DHEAS in the elderly was proportional to the decreased basal level (115), which is compatible with the concept of a diminished mass of responsive cells with maintained responsiveness of the residual cells.

D. 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.

1. 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 (116–118). But the reports are not consistent with some studies finding no significant variation or maximum levels rather in spring or summer (for review, see Ref. 117). 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 (73).

The circadian variation should not contribute substantially to the interindividual variability of serum testosterone levels as long as serum testosterone is being consistently evaluated in the first part of the morning (around 0700 to 1000 h). Moreover, although persisting to some extent, the circadian variation of serum testosterone is markedly blunted in the elderly (34, 38, 40, 63).

Because testosterone is being secreted episodically, one could assume that part of the between-subject variability in serum testosterone represents random effects underlined by the moment-to-moment intraindividual variation in serum testosterone. To some extent this is certainly the case, but moment-to-moment variations in circulating testosterone are rather limited and discrete pulses of testosterone are usually not discernible, at least not during daytime (119). In any case, in middle-aged men, single point measurements of testosterone have been found to reflect rather well the long-term hormonal levels (120), and we found that in 248 healthy community-dwelling men over age 70 yr, two single point measurements of total testosterone at a 1-yr interval were strongly correlated ($r = 0.82$) (73). Therefore, to apply single point measurements is an acceptable approach for the purpose of epidemiological studies. Nevertheless, individual elderly men have been reported to present week-to-week variations in serum testosterone and bioT, which could result in misclassification of men as having normal or low serum levels relative to the reference range if based on a single time point measurement (121).

2. Ethnicity and heredity. Heredity plays an important role as shown by studies in twins by Meikle *et al.* (122, 123), 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 (124). 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 (125).

Ethnic variations in serum testosterone have been reported, and in particular observations of slightly higher total testosterone and SHBG levels in men of African origin compared with Caucasian. These small differences of a few percent tend to disappear when full adjustments are made for body composition, including adjustment for some measure of abdominal adiposity. There are generally no differences in serum FT (126–128). No consistent differences are found in serum testosterone levels between Caucasians and men of Asian origin (129, 130); lower serum total testosterone, SHBG, and FT has been reported in a group of Pakistani compared with Caucasian and African-Caribbean men residing in England, part of the observed difference being again explained by differences in abdominal adiposity (131).

Recently, there has been considerable interest in a possible role of an AR gene polymorphism. The AR gene contains in exon 1 a polymorphic trinucleotide CAG-repeat, which encodes a functionally relevant polyglutamine tract of variable length. A CAG-repeat length exceeding the normal range of 15–31 results in a diminished AR transactivation capacity (132). In X-linked spinal and bulbar muscular atrophy (Kennedy's disease), the CAG-repeats in the AR exceed 40, and the clinical picture includes signs of mild androgen resistance (133–135). Evidence from *in vitro* studies indicates that androgen activity might also be affected by variations in AR CAG-repeat lengths within the normal range (136, 137). Clinical studies have associated shorter repeat lengths with higher prevalence of several androgen-sensitive diseases, including prostate cancer (138), although this is not confirmed in all studies; a polymorphic GGC-repeat encoding a polyglycine tract in the AR has also been associated with prostate cancer (139). An association of shorter AR CAG-

repeat length with greater longitudinal decline of serum testosterone and bioT levels has been reported for a subgroup of middle-aged men in the Massachusetts Male Aging Study (MMAS), although there was no association found between CAG-repeat length and baseline serum levels of either testosterone or FT, nor was there a consistent association with follow-up hormone levels (140). No association was found between the polymorphic AR CAG-repeat and sex steroid serum levels in a cohort of community-dwelling healthy men over age 70 yr in Belgium (141), in accordance with the lack of association between this polymorphism and serum testosterone levels in a study in Chinese and Australian men (142), in studies in German men (143–145), and in a study in Finnish men (146). As to the LH levels, which might be expected to vary according to differences in androgen sensitivity at the hypothalamic-pituitary level, there are no consistent findings with lack of association between AR CAG-repeat length and LH levels in some studies (140, 141), weak positive associations between repeat length and LH reported by others (125, 143), or even observations of a negative association in a Finnish cohort, although no longer significant after adjustment for age (146). From the whole of these studies, it can be concluded that the AR CAG-repeat polymorphism does not appear to contribute substantially to the determination of androgen levels in elderly men. On the other hand, as mentioned in other sections of this review, there have been reports of associations of the AR CAG-repeat polymorphism with clinical parameters modulated by androgen action.

In a cohort of elderly men in The Netherlands, serum total testosterone and bioT were not different in subjects with wild-type LH and those heterozygous for a polymorphic variant caused by point mutation-based substitutions of two amino acids ($Trp^{8}Arg$ and $Ile^{15}Thr$) in the LH β-subunit (147).

3. Fat mass and its distribution. Adiposity as assessed by the body mass index (BMI) [*i.e.*, body weight (in kilograms)/body height (in meters)^2] is an important negative determinant of total serum testosterone levels, mainly via its effects on SHBG levels (105). 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 (35, 48, 106–108, 131, 148–151). Similarly, a negative association of serum SHBG and total testosterone with leptin levels was observed (103, 152), this negative association being (103) or not being (152) maintained after adjustment for BMI. Overall, negative associations with serum testosterone levels tend to be most pronounced for indices of abdominal adiposity (48, 107, 108, 149, 153, 154).

Although in young and middle-aged men, moderate obesity (BMI $\leq$ 35 kg/m^2) affects mostly the serum SHBG and total testosterone levels, morbid obesity (BMI $>$ 35 kg/m^2), and mainly abdominal fat accumulation, also affects FT levels (106, 107, 148) as a consequence of alterations in the neuroendocrine regulation of testosterone secretion, characterized by a decreased mean amplitude of LH pulses (106). Nevertheless, also within the normal variation of adiposity in the population, negative associations with FT levels can be observed, in particular in the elderly (48, 103, 108, 152). Adiposity is also associated with lower DHEA and DHEAS (35), although a positive association between DHEAS and BMI has been observed in the oldest-old (155).

When considering the effects of body composition on the androgen status in elderly men, one should keep in mind the caveat that the interrelation between androgen status and body composition is probably bidirectional with, as discussed in later sections of this review, androgen deficiency and androgen treatment, respectively, having substantial and opposite effects on body composition and insulin sensitivity.

4. Diet. As far as the influence of diet is concerned, reports in the literature are rather divergent. In a study in elderly monks (34), plasma testosterone and FT levels were similar in vegetarian and nonvegetarian subjects. It has been reported (156) 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 (157–161), but FT levels may not be significantly different (159). 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 (162). Interestingly, low protein intake is known to be associated with low serum IGF-I levels (163), which can be hypothesized to play a role in the age-related increase of serum SHBG (35, 109, 110).

5. Stress. Stress evokes adaptive neuroendocrine reactions with, on the one hand, activation of the stress-responsive corticotropic, sympatho-adrenal, and somatotropic axes and, on the other hand, suppression of the gonadal axis through restraining of hypothalamic GnRH secretion (92, 164–167). One of several possible mechanisms underlying the latter inhibition of GnRH secretion may involve corticotropin-stimulated secretion of endogenous opiates (168–171).

Acute fasting for 48 or 84 h has been reported to result in a substantial reduction of serum testosterone in healthy men through reduced LH pulse frequency and amplitude (92, 164, 172), which can be reversed by pulsatile administration of GnRH (167) and may involve a specific metabolic signal rather than a nonspecific reaction to stress (173). Interestingly, elderly men appear to be relatively resistant to the metabolic stress of fasting compared with young men (92).

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 (174–179). 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 (180). As assessed in a small group of subjects, insulin-induced hypoglycemia re-

sulted 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 (34). 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 (34). 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.

6. Other lifestyle-related factors. Serum total testosterone and SHBG are reported to increase transiently during acute physical exercise of moderate intensity (181, 182), an effect that appears to result from hemoconcentration and decreased testosterone MRC (181, 183).

There is little information on the effects of dosed exercise programs on circulating androgen levels in elderly men, although such programs might have an effect on testosterone levels, in particular through changes in body composition and activity of the somatotropic axis. Deslypere and Vermeulen (34) found no consistent effect of a revalidation physical training program after myocardial infarction; Houmard *et al.* (184) observed no effects on serum androgen levels in middle-aged sedentary men of an exercise program that did result in significantly improved insulin sensitivity. Kraemer *et al.* (182) found a small increase of resting FT levels at the end of a 10-wk heavy-resistance training program in a group of eight men of 30 yr but not in men of 62 yr of age.

At all ages in adult men, serum testosterone and FT levels are 5–15% higher in (actual) smokers compared with nonsmokers (34, 35, 185–187). Smoking is also associated with higher DHEA and DHEAS serum levels (35, 187, 188).

Moderate alcohol consumption has no marked effect on serum testosterone (49, 162). Alcohol abuse, also in the absence of cirrhosis of the liver, accelerates the age-associated decline of serum testosterone and FT levels and is accompanied by increased estradiol levels (189–192).

A controversial issue is whether and how sexual activity influences mean serum testosterone levels; the data available is inconsistent and does not allow for a conclusion (193–196).

E. Contributory role of diseases and their treatment

As has been discussed in previous sections, aging *per se* induces a slow progressive decrease in plasma total and nonspecifically bound testosterone, with a substantial proportion of men over 65 yr who are in apparently good health presenting with serum levels below the reference range for young men. However, at all ages serum testosterone levels may be transiently or more permanently also affected by diseases or their treatment (41, 197–200). Considering that the incidence and prevalence of diseases and consumption of medication with possible adverse effect on androgen status increase with age, in daily practice age-related decline in serum testosterone is not uncommonly accentuated by concomitant disease. An exhaustive inventory of the effects of disease on the androgen status falls beyond the scope of this review, and we limit the discussion to a few examples that are potentially relevant to the situation in elderly men.

1. Acute critical illness. Acute critical illness, such as in patients with surgical trauma or myocardial infarction, is commonly associated with temporary, but often profound and prolonged decrease of serum testosterone levels (197, 201–203). The hypogonadism in critically ill men involves alteration in all compartments of the hypothalamo-pituitary-testicular axis, with observations of transient elevations of serum LH in the initial phase and of a state of hypogonadotropic hypogonadism during more prolonged illness (201, 202, 204–206).

2. Chronic systemic diseases. Both testosterone and SHBG tend to decrease in elderly men with diabetes mellitus (207). Testosterone levels were found to be lower in men over 60 yr with type II diabetes than in nondiabetic controls (154, 208), which is in line with a negative association of serum testosterone with adiposity and insulin resistance in nondiabetic men.

Most cross-sectional studies report lower or similar testosterone levels in patients with coronary artery disease (CAD) compared with controls (209–211). Similarly, inverse associations between serum testosterone levels and other measures of atherosclerosis have been reported (212, 213). In a longitudinal study, Zmuda *et al.* (32) found a more rapid age-associated decline of testosterone levels in patients at increased risk for CAD. However, in neither case-control studies nor prospective cohort studies could an independent association between endogenous testosterone levels and subsequent development of fatal or nonfatal CAD be observed (for review, see Ref. 214). An inverse correlation has been reported between (F)T levels and blood pressure (215, 216), possibly mediated by the abdominal obesity that is associated with atherosclerosis and increased blood pressure.

Chronic obstructive pulmonary disease (COPD) is often accompanied by decreased serum testosterone concentrations, also in the absence of systemic glucocorticoid treatment, with normal or decreased gonadotropin levels pointing toward hypothalamo-pituitary dysfunction; this is possibly the consequence of hypercapnea or of hypoxia (217–220). It has been reported that men with obstructive sleep apnea not uncommonly present with low morning testosterone levels, which can be reversed by treatment with nasal continuous positive airways pressure (221–223).

Patients with chronic liver disease, with or without hepatic cirrhosis, tend to present with hypogonadism characterized by decreased FT levels and increased serum concentrations of SHBG, androstenedione, and estrogens (224, 225); alcohol has an additive effect on the hypogonadism of cirrhosis (226). Hypogonadism is also a classical feature of hemochromatosis, which is predominantly the consequence of a pituitary lesion caused by the iron overload (227).

Hypogonadism is a common sequel of chronic renal failure (228), which is underlied by a complex pathophysiology. On the one hand, mean gonadotropin levels are usually elevated, probably mainly a consequence of an increase of plasma half-life (229). On the other hand, there are abnormalities in LH secretion resulting from altered GnRH release (228, 229), and there is also evidence for the existence of impaired Leydig cell function (229).

A variety of endocrine diseases are known to induce hy-

pogonadism, which includes primary testicular lesions, Cushing's syndrome, prolactinoma as well as other secreting or nonsecreting pituitary tumors. There is a broad overlap between the symptomatology of normal aging, of hypogonadism, and of hypothyroidism, the latter being itself a possible cause of hypogonadism (230). Thyrotoxicosis takes a special position in that it is characterized, even in the absence of evident clinical signs of thyrotoxicosis, by greatly increased serum total testosterone levels, secondary to a marked increase of SHBG levels, with generally normal levels for FT (104, 230, 231).

As to diseases of more particular concern in some countries or ethnic groups, it can be mentioned that men with sickle-cell disease can present with low serum testosterone levels (232) and that in men previously treated for leprosy, hypogonadism is not uncommon as a sequel of *Mycobacterium leprae*-caused orchitis (233–235).

3. Drugs. In the elderly, there is a rather high prevalence of use of medication and in particular frequent concomitant use of multiple drugs. Age-related decline of Leydig cell function, which may already be worsened by intercurrent disease may thus also be accentuated by use of drugs. A typical example of the latter situation is systemic administration of glucocorticoids in older men with COPD (236). Adverse drug actions on adult Leydig cell function and their underlying mechanisms have not been extensively studied. Here, we discuss only a few examples of potential adverse drug effects.

If only as a reminder, one has to mention here that the hormonal treatment of prostate cancer, the most common nondermatological cancer in men in Western countries, consists in suppression of endogenous testosterone production with use of a GnRH-analog and/or blockade of androgen effects by administration of an antiandrogen. As to the use of inhibitors of the 5α-reductase in men with benign prostate hypertrophy, treatment with finasteride results in slightly elevated serum LH and testosterone levels (237), but the treatment mitigates androgenic effects in those tissues that are largely dependent on local production of DHT, which can result in mild symptoms or signs of hypogonadism (238). Chemotherapy with alkylating agents, which has major effects on spermatogenesis, can also result in mild Leydig cell insufficiency (239, 240).

Systemic glucocorticoids have dose-dependent adverse effects on testosterone production, which may result from both direct testicular effects and inhibition of gonadotropin secretion (220, 236, 241, 242).

Opiates and cannabinoids suppress testosterone production through inhibition of gonadotropin secretion (243, 244). Similarly, LH secretion and Leydig cell function may be adversely affected by hyperprolactinemia during chronic use of neuroleptic drugs and related compounds (245). Ketokonazol inhibits the c17/c20 lyase, decreasing testosterone synthesis (246), whereas spironolactone reduces the 17 hydroxylase-lyase activity leading also to reduced testosterone biosynthesis (247). Several classes of antihypertensive drugs, including β-blockers, can interfere with normal erectile function, and hypertensive patients under treatment may often show a moderate reduction in serum testosterone levels (198, 248), but in view of the many confounding factors in these subjects, a drug effect on the testosterone levels cannot be considered as established.

F. Tissue levels of androgens and androgenic action

Although testosterone itself exerts androgenic and anabolic actions through binding to the nuclear AR in target cells, it is essentially a prohormone, being reduced to the more active androgen DHT in tissues expressing 5α-reductase (type II in the urogenital tract and hair follicles; type I in skin and liver), whereas a fraction of testosterone can be aromatized to estradiol in tissues expressing the cytochrome P450 aromatase enzyme. Hence, action of testosterone is the complex resultant of tissue availability and locally achieved testosterone concentrations, of local testosterone metabolism, of expression of AR and/or ERs, as well as the expression of a number of coactivators and repressors of these receptors. Each of these determining factors of testosterone action can be differentially regulated in the tissues, thus offering a close to unlimited potential for differential regulation of sex steroid action in the tissues. This complexity of testosterone action should be kept in mind when discussing clinical implications of declining androgen levels in aging men and possible merits and risks of androgen treatment to the elderly.

Both the AR and ER (ERα and/or ERβ) are expressed in a wide range of tissues. The AR is found in the highest concentrations in male accessory sex organs (249) and in some areas of the brain, whereas lower concentrations of AR are measured in skeletal muscle (250), in the heart and vascular smooth muscle (251), and in the bone (62). Testosterone and DHT bind to the same receptor, but the affinity of DHT for the AR is greater than that of testosterone and in many tissues DHT mediates most androgenic effects of testosterone. In muscle, however, testosterone itself is the active androgen, 5α-reductase activity being extremely low and no DHT formed (252).

Androgen concentration in target tissues depends on plasma concentration of bioavailable androgen, local androgen metabolism, and the presence of AR. As expected, total androgen (testosterone + DHT) concentration is highest in the prostate and scrotal skin, and higher in pubic skin than in striated muscle. In prostate and scrotal skin, DHT is quantitatively by far the major androgen, the DHT concentration being 5–10 times higher than that of testosterone; in muscle DHT levels are, as expected, extremely low (253) (Table 1). In the prostate, induction by DHT of type 2 5α-reductase has as a consequence that almost all androgenic effects are exerted by DHT, enhancing the AR-mediated androgen effects (254).

Few data are available on the influence of age on androgen concentrations in the tissues, but available studies show the expected age-associated decrease of androgen levels in different tissues, albeit not in scrotal skin (252, 255). Krieg *et al.* (256) observed an age-related decrease of DHT concentration in the epithelium in the prostate and a substantial increase with age of estrogen levels and of the estrogen/androgen concentration ratio, particularly in the stroma of the prostate.

The concentration of AR is influenced by androgens (increase), estrogens (increase of AR in prostate), and aging,

TABLE 1. Tissue levels of androgens and influence of age

Tissue[a,b]	Age (yr)	N	T (ng/g)	DHT (ng/g)	Adiol (ng/g)
Scrotal skin	20–39	8	1.64 (0.56–2.92)	6.82 (2.41–13.85)	4.48 (1.38–8.83)
	60–82	8	1.77 (0.39–2.89)	6.72 (1.28–9.09)	3.07 (1.17–4.41)
Pubis skin	20–39	8	1.75 (0.44–4.90)	1.96 (0.58–5.92)	2.16 (0.88–6.91)
	60–82	8	0.83 (0.51–1.51)	0.88 (0.51–1.31)	0.83 (0.47–1.02)
Cardiac muscle	35 ± 12	22	1.86 ± 0.17	0.49 ± 0.08	0.51 ± 0.07
	74 ± 8	16	1.01 ± 0.12	0.47 ± 0.08	0.36 ± 0.09
Lung tissue	34 ± 12	18	2.42 ± 0.34	0.96 ± 0.24	0.89 ± 0.09
	75 ± 8	14	1.07 ± 0.15	0.53 ± 0.09	0.44 ± 0.07
Striated muscle	20–89	16	0.46 ± 0.05	0.25 ± 0.03	0.29 ± 0.04
Prostate (BPH)	60–76	24	0.52 ± 0.05	6.12 ± 0.27	0.87 ± 0.10

Data represent mean (range) or mean ± SEM. Adiol, Androstanediol; T, testosterone. [Adapted from Refs. 252, 253, and 255.]
[a] Postmortem samples.
[b] All values, nanograms per gram wet weight.

which has been reported to be accompanied by a decrease of AR concentration in different tissues (257–261). Androgen sensitivity could be modulated by functional AR receptor polymorphisms, such as the aforementioned variation in functionally important polyglutamine and polyglycline tracts, encoded by a polymorphic trinucleotide CAG-repeat and GGC-repeat, respectively, contained in exon 1 of the AR gene (136–139).

G. Androgen metabolism

As discussed in *Section II.F*, 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 biotransformed 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/$\Delta^{4,5}$ isomerase, the subsequent metabolism being identical to that of testosterone. The end metabolites of endogenous androgens, *i.e.*, androsterone, etiocholanolone, and 5α/5β androstane-3α,17β 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 (262). Androstanediol glucuronide (ADG) is considered by many as an important parameter of androgen action in women (263, 264), but in males its major precursor being testosterone (70%), with 30% deriving from DHEAS (265), determination of ADG does not offer much interest. The urinary excretion of ADG decreases significantly with age (266); the ratio of urinary 5α/5β metabolites decreases with age, a consequence of a decrease of 5α reductase type 2 activity (267).

III. Clinical Significance of the Age-Associated Decrease in Androgen Levels

A. Introduction

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.

B. 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. The latter changes are frequently accompanied by signs of altered tone of the autonomous nervous system as manifested by nervousness, insomnia, and sometimes hot flushes. The analogy with the general symptomatology of hypogonadism in young males is striking: impaired virilization with poor development of sexual body hair and beard growth, decreased bone and muscle mass with decreased physical strength, weakness, decreased libido, and often erectile dysfunction, abdominal obesity, and difficulty with concentration.

This symptomatology in the elderly develops, however, slowly and progressively, the symptoms being subtle, variable, and not specific. Hence, the clinical symptomatology does at best only suggest the possibility of a hypoandrogenic state in the elderly.

C. 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 (268, 269) and the spine (270, 271). Moreover, in older men the consequences of fractures in terms of morbidity and mortality appear to be more severe than in their female counterparts (272, 273). Acquired profound hypogonadism in men induces high bone turnover and accelerated bone loss (274), which has also been confirmed to be the case in the elderly (275, 276). However, whether and in how far an age-related partial androgen deficiency may be instrumental in senile osteoporosis in men is not definitely established.

Although the complex role of testosterone in the regulation of bone metabolism is yet to be fully elucidated, a large body of evidence allows us to conclude that besides direct androgen actions, aromatization to estrogen plays an important role in the regulation of both the acquisition of adult bone mass and the preservation of adult skeletal integrity (62, 63). Indeed, cross-sectional studies, in which age and BMI (or body weight) are major confounders, have yielded inconsistent results as to the association of serum testosterone levels with prevalent BMD in elderly men, with some studies failing to show an independent association (277–279), whereas others did show weak but significant positive correlations, in particular with FT or bioT (72, 280–284). On the other hand, in a series of recent cross-sectional studies, multivariate analysis consistently indicated that free or bioavailable estradiol is a better predictor of prevalent BMD in elderly men than FT or bioT (72, 283–291). Biochemical indices of bone turnover increase moderately with aging in men and are inversely related to prevalent BMD in the elderly (292), with markers of bone resorption more clearly (negatively) associated with serum levels of estradiol than with those of testosterone (63, 284, 289, 291, 292), although correlations are generally weak.

Cohort studies have shown that bioavailable estradiol is negatively associated with prospectively assessed bone loss, without independent association of serum (bioavailable) testosterone (284, 290, 293). Moreover, prospectively assessed bone changes in elderly men were also found to be associated with a polymorphism of the CYP19 gene that encodes the aromatase enzyme, independently of serum estradiol levels, suggesting indirectly that local aromatization of testosterone in bone tissue might play a role (290). Although there has been a report of association of a CAG-repeat polymorphism of the AR with BMD assessed by ultrasound in men aged 20–50 yr (143), in community-dwelling men over age 70 yr, no association was found between this polymorphism and either BMD or biochemical indices of bone turnover (141).

The important role of aromatization of testosterone to estrogen in the regulation of bone metabolism in elderly men has been further elegantly demonstrated in a short-term intervention study with selective manipulation of testosterone and estradiol levels (294). There is evidence indicating that there may be a threshold level for the association of bioavailable estradiol with bone loss and indices of bone metabolism (287, 293, 295–297), although other studies did not demonstrate such a threshold (290).

As to the association of sex steroid levels with fracture risk in elderly men, little data are available. In case-control studies, there was a higher prevalence of low serum testosterone in men recruited after a hip fracture (298–300), but testosterone levels assessed after a traumatic event should be interpreted with caution. In the Rancho Bernardo study, lower estradiol levels, but not serum testosterone concentrations, were associated with a higher prevalence of vertebral fracture in older men (301). In a case-control study in men aged 67.7 ± 6.8 yr as part of the Rotterdam Study, there was no significant association between vertebral fracture and either bioavailable estradiol or bioT (302). There was a preliminary report from the Mr. OS study in 5995 community-dwelling men 65 yr or older of an association of incident fracture risk with both bioT and bioavailable estradiol, with only the latter assocation being apparently mediated by a lower BMD (303). In community-dwelling men over age 70 yr, an aromatase gene polymorphism, associated with longitudinal changes in BMD, was also significantly associated with self-reported clinical fractures at the spine, hip, and/or wrist and with the occurrence of these fractures in their first-degree relatives, but there was no association of fracture history with circulating bioavailable estradiol (290).

In summary, the evidence suggests that 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, the skeletal effects of a relative testosterone deficiency in the elderly being modulated by aromatase activity, which in turn is affected by factors such as adiposity and heredity.

2. Body composition. Aging is associated with important changes in body composition (108, 304, 305). In healthy men, fat mass was found to increase from around 22% of body weight in young men to around 30% in the elderly, lean body mass being 30% lower in the elderly group (108). Similar changes with a decrease of lean body mass and increase in fat mass are observed in hypogonadal men compared with age- and BMI-matched controls (306). It thus seems logical to suspect a role of the decreased androgen levels in the changes in body composition seen in elderly men.

In healthy men, there is a negative correlation between serum testosterone and FT with visceral fat (307), and in a study involving 61 middle-aged men and 271 elderly community-dwelling men aged 70–85 yr (108), 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 (72, 192, 305). Khaw and Barrett-Connor (149) 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, sc fat (308). Moreover, testosterone stimulates lipolysis and thus reduces fat storage in the fat cells (304).

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, as discussed in *Section II.D.3*, increased adiposity is itself partially responsible for a decrease of testosterone levels (35). Moreover, decreased GH levels, as observed in elderly males (309–313) 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 (312).

The reduction of muscle mass by about 30% between ages 30 and 80 yr (313–315) is accompanied by a proportional decrease of muscle strength (316). This decreased muscle strength contributes to frailty and is a risk factor for falls, hip fractures, and loss of independent living conditions.

Again, the similarity with the occurrence of low muscle mass in hypogonadal young men raises the hypothesis that the age-associated decrease in androgen levels may be in part instrumental in the sarcopenia of elderly men. Few data concerning the correlation between endogenous androgen levels and muscle mass in elderly men are available, however. In an already mentioned study (108) involving middle-aged and elderly community-dwelling men, no correlation was found between testosterone or FT levels and lean mass. Similar negative findings were reported by van den Beld *et al.* (72) and by Roy *et al.* (317) in men aged 20–90 yr old, who observed nevertheless a positive association of FT levels with muscle strength. Szulc *et al.* (291) in a cross-sectional analysis in men 51–85 yr found that low FT is associated with lower muscle mass, functional impairment in the legs, and occurrence of falls in the past year. In institutionalized healthy elderly men, Abbasi *et al.* (318) observed a correlation between testosterone levels and severity of sarcopenia. Also, Baumgartner *et al.* (319) observed a positive association of FT with muscle mass, but not with muscle strength.

In summary, the literature indicates that the age-related decline of androgen levels does affect body composition, although the data on muscle mass and strength is limited and not consistent. Indeed, in aging males the interrelations between FT and muscle mass or strength are obscured by confounding effects of relative physical inactivity as well as by the effects of the age-associated decrease of somatotropic stimulation.

3. Atherosclerosis and CAD. Atherosclerosis and CAD increase almost exponentially with age and are much more frequent in men than in premenopausal women (320), the gender gap narrowing after the age of 50 yr (321, 322). This gender gap with male preponderance is observed in all countries, notwithstanding widely divergent rates in cardiovascular mortality (322, 323). A gender difference is also observed in the plasma lipid profile: before menopause, women have higher high-density lipoprotein-associated cholesterol (HDL-C) and lower low-density lipoprotein-associated cholesterol (LDL-C) and lipoprotein (a) levels than men, whereas women with hyperandrogenism show a higher risk lipid profile (321, 324). In men, suppression of plasma testosterone with GnRH analogs increases HDL-C (325, 326), an effect that is abolished by coadministration of testosterone (326, 327). All this has led to the common belief that androgens are harmful and estrogens beneficial.

Review of the literature, however, does not provide convincing evidence that the gender difference can be explained by distinctive patterns of endogenous sex hormones (for review, see Refs. 322 and 323). Indeed, of 32 cross-sectional studies on the relationship between endogenous testosterone levels and CAD (209), 16 showed lower testosterone levels and 16 showed similar levels in patients with CAD compared with controls. In more recent studies, Barrett-Connor (328), English *et al.* (329), as well as Hak *et al.* (212) observed a consistent inverse relationship between endogenous plasma testosterone levels and CAD. In a study involving 403 men aged 73–94 yr, van den Beld *et al.* (213) observed that serum testosterone levels, adjusted for age, were inversely correlated with intima media thickness (IMT) of the carotid artery (213). Although many of the subjects in the latter study suffered from angina pectoris, recent myocardial infarction, or diabetes mellitus, which might be responsible for both the decreased testosterone levels and CAD, the authors showed nevertheless that the associations of IMT with testosterone levels were as powerful in subjects free of CAD as in subjects with prevalent CAD. In a subgroup of 195 of these men, lower FT was also associated with greater progression of IMT, independently of cardiovascular risk factors (330).

Prospective cohort studies (32, 212) and case-control studies (214, 331, 332) involving thousands of patients did not show correlations of testosterone with CAD or a predictive value of testosterone levels for CAD (for review, see Refs. 322 and 323).

As to the correlation of testosterone levels with risk factors for CAD in men, data in the literature suggest an inverse correlation between endogenous plasma FT or bioT and total cholesterol as well as LDL-C, fibrinogen, and plasminogen

activator type 1 (for review, see Refs. 322 and 323). Moreover, most studies (333–335) suggest a highly significant positive correlation between total testosterone and FT on the one hand and serum HDL-C and apoprotein A on the other hand. In a recent study involving a group of 526 men, aged 20 to 89 yr old, Schatzl *et al.* (336) found a negative correlation between FT and total cholesterol, triglycerides, and glucose levels, but this was not corrected for major confounders.

In a multivariate analysis of the association of both testosterone and estradiol levels with cardiovascular risk factors in a cohort of 715 middle-aged men, Van Pottelbergh *et al.* (337) observed that FT was significantly, positively associated with HDL-C and apoprotein B, whereas free estradiol was a stronger predictor of apoprotein E.

Association of higher endogenous testosterone levels with more favorable lipid profiles has been observed in men of different ethnic origin: Ooi *et al.* (338) reported similar results in Chinese men, whereas Miller *et al.* (339) reported a positive correlation between testosterone and HDL-2 cholesterol in Trinidadians of African or Indian descent.

There are, nevertheless, indications that the relationship between serum testosterone, lipid profile, and CAD may be modulated by genetically determined variation of androgen sensitivity (145, 340), thus complicating the interpretation of findings on association between endogenous androgen levels and serum lipid profile.

Androgens, moreover, modulate vasoreactivity by endothelium-dependent and -independent mechanisms involving genomic and nongenomic pathways. Physiological testosterone concentrations restrict vasodilatation via the genomic pathway, whereas supraphysiological concentrations may have nongenomic vasodilatatory effects on vascular smooth muscle in all arterial beds, blocking membrane calcium influx (341), but the high (micromolar) concentration required for the latter effect casts some doubt about the physiological significance of these responses. Androgen substitution in hypogonadal men was found to reduce vascular reactivity (342).

As to blood pressure, epidemiological findings show that testosterone and blood pressure are inversely correlated, but it is not established whether hypertension is the cause or the consequence of low testosterone levels (215, 216).

In conclusion, available data suggest that moderately low testosterone levels as observed in elderly males are accompanied by an increased frequency of atherosclerosis and CAD. Whether the decreased FT or bioT levels play a direct causal role in this pathology is doubtful. In elderly males, low testosterone levels could be a consequence of the increase in abdominal fat, which is accompanied by increased insulin levels, favoring the development of atherosclerosis and CAD, and in some studies (343), but not in others (330), the correlation between FT levels and cardiovascular risk or atherosclerosis disappeared after correction for BMI or abdominal fat.

It has been reported that low DHEA(S) levels, as found in the elderly, are associated with increased cardiovascular morbidity and mortality (344–351). However, several other studies failed to detect such associations (214, 332, 352, 353) and neither Baulieu *et al.* (354) nor van den Beld *et al.* (213) found supporting evidence for a potential cardioprotective role for DHEAS. In the Helsinki Heart Study of middle-aged dyslipidemic men, higher DHEAS levels were associated with increased risk of CAD (332). It should be realized that DHEAS levels are highly population dependent: Japanese men living in Japan have the lowest DHEAS levels and the lowest risk of coronary heart disease. Again, interpretation of these results is complicated by the strong age dependency of plasma levels and the fact that overweight men have lower DHEAS levels, whereas alcohol and smoking (55, 187) are associated with higher DHEAS levels. Because low DHEAS levels appear to be associated in males with mortality of all causes (355), it could be considered that low DHEAS levels are a nonspecific marker of poor health (356), but literature data does not support the idea that DHEAS levels are predictors of CAD or that DHEA has a significant antiatherogenic action.

4. Sexual function. Aging in men is accompanied by a decrease in libido and sexual activity, mean coïtal frequency decreasing from about four times a week at age 20–25 to two times a month at age 75–80 yr (90). Nevertheless, only 15% of men over 60 yr deny any sexual activity (357).

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)] (358). 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) (358–360). Hence, it is not surprising that the correlation of libido with plasma testosterone levels is rather poor (361, 362). Nevertheless, Tsitouras *et al.* (363) 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.* (364) reported that men with hypoactive sexual desire had lower testosterone levels than controls, and Pfeilschifter *et al.* (110) 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 (365, 366).

Frequency of erectile dysfunction increases dramatically with age. Androgens, which act centrally as well as peripherally (367), where testosterone stimulates nitric oxide synthase in the corpora cavernosa (368), 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 (369, 370). 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 (371), the most prevalent cause of erectile dysfunction being atherosclerotic pelvic arterial insufficiency (372). There is good evidence that, whereas NPT is androgen dependent (371), erections in response to erotic fantasies or visual stimuli are largely androgen independent

(362, 373, 374). Indeed, audiovisual sexual stimulation, such as erotic movies can induce complete erectile responses in young hypogonadal men. Nevertheless, both duration and maximal rigidity are significantly increased after androgen treatment, suggesting a partial androgen dependency of "psychogenic" erections (362, 374). In men with marked hypogonadism, frequency, amplitude, and rigidity of the erections are significantly reduced, but they remain normal at moderately decreased androgen levels (375) and a threshold level of 200 ng/dl has been suggested for sleep-related erections (360). This probably explains why in most studies in elderly men no correlation was observed between erectile dysfunction and serum testosterone levels (376–378). Indeed, few healthy elderly men have serum testosterone levels below this value; in a group of 172 healthy men aged 50–70 yr we found that only 10 had a serum testosterone level below 250 ng/dl (A. Vermeulen, unpublished data).

The MMAS (376) in 1709 free-living men aged 40–70 yr at baseline, failed to show a relationship between erectile dysfunction and FT, gonadotropins, or prolactin levels, in agreement with observations by Rhoden *et al.* (377), whereas Korenman *et al.* (378) observed that the age-associated decrease in FT was not different in men with and without impotence. Surprisingly, in the MMAS (376) a correlation between prevalence of severe erectile dysfunction and DHEAS levels was observed, concentrations below 50 μg/dl being associated with a prevalence of 16% of complete impotence, against 6.5% when DHEAS levels were above 50 μg/dl and 3.4% at levels 100 μg/dl or higher, and this after correction for age; moderate degrees of erectile dysfunction were independent of DHEAS level. The latter findings in the MMAS might be related to the fact that DHEAS is an aspecific marker of poor health.

In summary, it is presently not established that age-associated decline of testosterone in healthy men contributes substantially to decreased libido and sexual activity in the elderly male population. As to erectile function, it may be concluded that, except for the few cases of erectile dysfunction due to pituitary or testicular pathology, erectile dysfunction in elderly men is largely nonhormonal in origin. Indeed, besides hypoandrogenism and hyperprolactinemia, many nonhormonal factors such as diabetes mellitus, atheromatosis, alcoholism, polyneuropathy, or renal insufficiency may be a cause of erectile dysfunction, whereas transient dysfunction may be caused by stressful situations, socioeconomic problems, acute infections, and a variety of drugs, in particular antihypertensive, psychotropic, and opioid medications.

5. Erythropoiesis. Men have higher hemoglobin and red cell mass than women (379), differences that only become apparent after puberty (380) and are independent of menstruation because they persist when considering young hysterectomized women (380). Elderly men tend to have a similar or slightly lower hematocrit than young men (381). An association between endogenous serum androgen levels and indices of erythropoiesis in elderly men has not been documented.

6. 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 (382).

In healthy young men, positive relationships have been observed between endogenous plasma testosterone levels and visual-spatial orientation (383, 384), but other studies have failed to find such an association (385–387).

Patients with isolated hypogonadotropic hypogonadism show an impairment of spatial abilities (387, 388), which is improved by androgen treatment (389, 390).

As to the effects of endogenous testosterone levels on cognitive functions in elderly males, Morley *et al.* (390) reported a significant correlation of the endogenous testosterone levels with visual and verbal memory, whereas in the Rancho Bernardo study (391), a higher bioT was significantly associated with better long-term verbal memory and score for a cognitive screening test. Yaffe *et al.* (392) 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 (393). 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 (394). 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 (395).

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.* (396) 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.* (355) 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.

7. 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 (397) reported depressive subjects to have lower testosterone levels than controls. Based on analysis of sub-

groups of subjects from the MMAS study, Seidman *et al.* (398) found lower serum testosterone levels in elderly men with dysthymic disorder but not in those with major depressive disorder, and they also reported that the relationship between testosterone levels and depression may be modulated by the CAG-repeat length polymorphism of the AR gene (398). From a review of the literature on testosterone and depression in aging men it was concluded that the available data suggest, but do not demonstrate that testosterone secretion may be reduced in some men with major depression (399). Recently, in a historical cohort study in a health care setting for U.S. veterans, hypogonadism was associated with increased incidence of depressive illness, which might relate to comorbidity (400).

In 856 men aged 50–89 yr participating in the Rancho Bernardo Study (401), bioT was significantly inversely associated with a depressive mood score as assessed with the Beck Depression Inventory, independently of age, weight, or physical activity. The MMAS study, which included 1709 male subjects 39–70 yr old, showed that an androgen deficiency pattern was accompanied by low dominance; moreover, in 25 men with true depression, bioT was 17% lower than in the rest of the group (402). In men 50–70 yr old, who participated in a screening program on prostate cancer and "andropause," FT was inversely correlated with depressive symptoms score according to the Carol Rating Scale, but was not related to threshold scores considered significant for depression (403). Several other studies (404–407) failed to find an association between FT or bioT and depressive scores, whereas in contrast Perry *et al.* (365) even reported that declining bioT levels were associated with lower levels of depressive symptoms on the Hamilton Depression Scale in men 55–75 yr old.

Taken together, available evidence does not indicate that the age-related decline in testosterone is a risk factor for clinically significant depression, although a role in depressive mood cannot be excluded.

8. 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 (366, 408). Neurovegetative symptoms such as hot flushes may be more common in elderly men than generally suspected (409), but an association with the endogenous sex steroid levels has not been established in otherwise healthy elderly men.

D. Summary

Summarizing the data concerning the association of FT or bioT levels with clinical signs and symptoms in elderly males, it is manifest that the clinical significance of partial androgen deficiency in elderly men remains unclear. Nevertheless, in many instances there does exist a weak, but statistically significant correlation between some of the aging symptoms and plasma testosterone levels, which generally tend to persist after correction for major confounders such as age and obesity. In any case, it is evident that androgen levels are only one of the many factors determining the symptomatology of elderly men. Moreover, it may be questioned whether a single point measurement may reliably reflect the androgen status in preceding years as a possible determinant of the prevailing clinical status of the subject at the time of investigation. Anyway, the hormone blood levels are at best imperfect parameters of testosterone action in the tissues. Overall, it seems reasonable to assume that partial androgen deficiency can be a contributory factor in some of the clinical changes in aging men, although more investigation is obviously needed before this issue can be settled and the contribution of androgen deficiency more precisely delineated.

IV. Diagnosis of Androgen Deficiency in the Aging Male

A. Introduction

Given that the signs and symptoms suggestive of androgen deficiency in aging males are not specific, diagnosis of androgen deficiency should evidently not be based solely on the clinical picture, and additional biochemical evidence is required for its ascertainment. However, in view of the still unresolved issue of what should be considered "physiological" or "optimal" androgen levels in the elderly, in many cases a margin of uncertainty will persist. Therefore, diagnosis should preferably be based on an appropriately conservative evaluation of the convergence between clinical and biochemical findings.

B. Clinical evaluation

A number of questionnaires are being used in clinical or epidemiological settings to help describe a variety of symptom clusters that are clinically relevant to elderly men, such as questionnaires on self-perceived health status, on depressive mood or depression, on cognitive function, on urinary symptoms, on erectile function or on coping with activities of daily living. There are also several questionnaires that are explicitly or implicitly proposed by their proponents as tools to summarize or evaluate symptoms of androgen deficiency in aging men. The Androgen Deficiency in Aging Males (ADAM) questionnaire has been developed by Morley *et al.* (410) as a screening tool for identifying middle-aged and older males with testosterone deficiency. This simple self-administrated questionnaire consists of a set of 10 questions that are to be answered dichotomously by "yes" or "no" and pertain to present or absent perception of decreased libido, lack of energy, decrease in strength, loss of height, decrease in enjoyment of life, feeling sad and/or grumpy, less strong erections, deterioration in the ability to play sports, falling asleep after dinner, and deterioration in work performance. In a group of 316 volunteering Canadian physicians with mean age of only 52 yr (range, 40 to 82 yr), the questionnaire had a sensitivity of 88% and a specificity of 60% to identify subjects with low serum bioT defined in this study as a level below 70 ng/dl as seen in 25% of the study group. Legros and Delhez (411), using a French translation of this questionnaire in 754 men aged 50–70 yr (mean, 59.5 yr) who were taking part in a prostate cancer screening and volunteered for an additional andropause evaluation (participation rate, 25% of

the men taking part in the cancer screening and 3% of the total target population), observed a sensitivity of 80% but a specificity of only 32% to identify FT below the range for young men (*i.e.*, 7 ng/dl). This questionnaire evidently lacks specificity, with part of the false-positive tests being associated with symptoms of depression (403).

The Aging Male Symptoms scale, based on subjective evaluation of symptomatology, was developed by Heinemann *et al.* (412) to help describe and quantify the clinical syndrome of andropause and was not intended as a screening tool for androgen deficiency and was not validated against androgen levels by the authors, but it has been proposed as an outcome measure for treatment of androgen deficiency (413). Using this scale in 161 healthy, ambulatory, elderly men aged 74–89 yr, T'Sjoen *et al.* (366) failed to find any correlation of a global score or of any subscore for the Aging Male Symptoms scale with serum levels of either FT or bioT, in agreement with findings by others (408, 414), suggesting that in community-dwelling ambulatory elderly men male climacteric symptoms are not predictive of the prevailing androgen levels. Whereas the latter scale is based on subjective symptomatology, Smith *et al.* (415) constructed a self-administered eight-item screener for testosterone deficiency in aging men that is based on age, BMI, occurrence of diabetes, asthma, and headache on sleep pattern, dominance preference, and smoking. This questionnaire, which takes into account aspects of comorbidity, has a similarly low specificity of only 49% for a sensitivity of 75% (positive predictive value between 28 and 52%). It can thus be concluded that presently available questionnaires have a low specificity for predicting serum testosterone in elderly men and cannot contribute to the diagnosis of partial androgen deficiency in the elderly. Furthermore, in the present state of the art, their widespread use as a screening tool to direct men for additional biochemical evaluation should probably be discouraged.

Although clinical examination may point toward specific causes of hypogonadism, there are no pathognomonic findings for age-related partial androgen deficiency. In a study in healthy elderly men over age 70 yr, combined testicular volume was decreased by about 20% with a combined testicular volume of 14.3 ml as best cut-off having a sensitivity of 46% and a specificity of 79% to predict a bioT level below the range for young men (89).

C. Biochemical evaluation

As to biochemical parameters of androgen deficiency in elderly men, there is no clinically useful biochemical marker of tissue androgen action, so that one has to rely upon measurement of testosterone concentrations in the systemic circulation. It is not known, however, whether androgen requirements in the elderly are similar, lower or higher compared with those in young men. There are indications of a greater sensitivity of some tissues with, in particular, greater responsiveness of the elderly to negative feedback suppression of LH secretion by androgens (95, 96, 99, 100) (Fig. 6). Findings in rodents and humans also indicate the possibility of decreased androgen sensitivity in some tissues as suggested by observations of age-related decreases of AR concentrations (257, 258, 416). Moreover, there is clear evidence that testosterone requirements differ according to the considered tissue. Finally, the large interindividual variations of FT and bioT levels represent another problem: might a decrease of testosterone levels in an individual from, *e.g.*, 1000 ng/dl as a young adult to 500 ng/dl in old age, a value still well within the normal range for the young, constitute an androgen deficiency for this particular person? In other words, is it at all possible to define a lower cut-off value of normalcy that is applicable to all subjects? From the discussions in previous sections (see *Section II.D.2*), it is obvious that there are individual differences in the relationship between testosterone blood levels and androgen effects. Nevertheless, it has also been illustrated that for at least some physiological actions of testosterone, such as those pertaining to sexual function, there is a safety margin between the lower limit of the physiological range of serum testosterone and the minimal requirements for normal functioning.

Among the proposed measurements of different fractions of blood testosterone, *i.e.*, total testosterone, FT or bioT, there are in at least some clinical situations differences as to how well they reflect the testosterone available to the tissues for biological action. Nevertheless, none of the measurements of circulating testosterone can claim to assess androgen action in the tissues, which is modulated by complex cellular processes. This limitation also holds true for the more recently developed recombinant cell bioassays (417) that are highly sensitive and may offer the advantage to integrate androgenic activity exerted by testosterone as well as other circulating androgens.

In the absence of a clinically useful parameter of androgen activity, it is difficult to determine a valid lower cut-off value for serum FT and bioT to ascertain the diagnosis of partial androgen deficiency and in the absence of convincing evidence for clinically relevant changes in androgen requirement in the elderly it can be proposed, as a pragmatic interim solution, to apply for the elderly the same reference range for serum FT and bioT as in young men.

In this context, it is interesting to note that Swerdloff and Wang (418), upon treatment with testosterone gel for 180 d, observed a similar increase in lean body mass and BMD and decrease in fat mass in 52 elderly men compared with 119 young men with serum testosterone level of less than 10.4 nmol/liter (300 ng/dl) at entry in the study.

Based on data obtained in large groups of healthy, nonobese men, the lower limit of the normal range is generally considered to be around 315 ng/dl (11 nmol/liter) for total testosterone and around 6.5 ng/dl (0.225 nmol/liter) for FT (20), corresponding to a bioT of around 140 ng/dl (5 nmol/liter) (89). Most authors use similar values (31, 280, 419, 420). Using these limits, less than 1% of healthy men aged 20–40 yr but more than 20% of men over 60 yr old have subnormal total testosterone levels, a percentage that is slightly higher when using FT (Fig. 5). Interestingly, the biochemically defined threshold of 315 ng/dl (11 nmol/liter) agrees well with the threshold for androgen deficiency symptoms recently reported by Kelleher *et al.* (421).

Although there is no objective reference point available to help settle the issue, the alternative solution to use rather an age-specific normal range as suggested by some authors (200, 336) would tend to imply that normal aging is by definition

not accompanied by hypogonadism, which is doubtful, and poses both practical and conceptual problems as to the selection criteria for inclusion of elderly subjects when establishing such an age-specific reference range. In this context, it might be worthwhile for future validation to consider a more objective and descriptive approach that aims to situate the testosterone level in an individual relative both to men of the same age group and young men; thus both as a Z-score, *i.e.*, the units of SD differences from the mean for age, and as a T-score, *i.e.*, the units of SD difference from the mean for young men (*e.g.*, between 20 and 40 yr). Although not solving the issue of diagnostic threshold, such an objective descriptive approach would allow us to more clearly define the testosterone level of subjects that are included in controlled (multicenter) intervention trials and thus to better identify from results of clinical trials to what segment of the general male population a proposed intervention might be applicable.

D. Practical approach to diagnosis

It is evident that in the absence of a reliable parameter of androgen bioactivity the lower normal limit of serum testosterone remains more or less arbitrary. Therefore, the diagnosis of partial androgen deficiency in elderly males, and certainly the decision to implement any potentially harmful intervention, should be approached with pragmatism and appropriate reserve.

Diagnosis should be based on the convergence of clinical symptoms and subnormal testosterone levels. The latter should be frankly low as measured in blood sampled in the morning (before 1000 h) and confirmed on a second occasion, preferably separated by a few weeks such as to allow for recuperation after eventual transient causes of hypogonadism. Although total testosterone will provide adequate information in many cases, assessment of FT or bioT should be preferred in situations characterized by substantial changes in SHBG levels. Taking into account the analytical interlaboratory variation of serum FT or bioT, each laboratory should assess its own lower limit of normal (422). As to the clinical picture, in view of its low specificity and the high prevalence of symptoms possibly associated with hypogonadism in the elderly population, one should avoid suggesting or soliciting symptoms, as may be the case with the use of screening questionnaires. In fact, when applying a combined diagnostic strategy based on a questionnaire and a lower cut-off for serum FT in young men to the data from the MMAS study, Araujo *et al.* (423) calculated a projected prevalence of androgen-deficient men as high as 2.4 million among 40- to 69-yr-old U.S. males, with as many as 481,000 incident new cases per year.

There is presently no evidence that the measurement of serum concentrations of other androgens than testosterone, including DHT, androstenedione, 3α-5α ADG, or DHEAS, can contribute to the diagnosis. Finding of an elevated serum LH together with a low serum FT or bioT should be considered as additional evidence in support of the diagnosis of androgen deficiency. However, in view of the age-related alterations in LH secretion, an elevated LH is not a prerequisite for the diagnosis, whereas conversely the diagnosis of androgen deficiency in elderly men cannot be based on an isolated elevation of LH without concomitant low serum testosterone. Measurements of LH after stimulation with GnRH may help to exclude secondary hypogonadism in elderly men (424). Along the same lines, finding of a low testicular volume can contribute to the diagnosis, but this criterion has low sensitivity (89).

V. Androgen Treatment in Elderly Men

A. Introduction

When considering therapeutic trials with androgen administration to elderly men, one can distinguish among three major types of possible studies, depending on the therapeutic goals. Firstly, short-term treatment (weeks or months) may be intended to prevent or alleviate frailty in particular clinical situations that are known to adversely affect general health and may or may not be accompanied by transient hypogonadism. A typical example would be androgen treatment in elderly men undergoing surgery or after hip fracture. In a second type of treatment, one may want to achieve longer-term specific anabolic effects in elderly men that are not necessarily hypogonadal, *e.g.*, androgen treatment to prevent or mitigate sarcopenia or senile osteoporosis. In a third type of studies, longer-term androgen administration is intended as "substitution therapy" in elderly men that have been selected on the basis that they are judged to be androgen deficient, with the goal to improve quality of life by preventing and/or alleviating particular symptoms believed to be at least in part the consequence of androgen deficiency. The chosen endpoints for the latter studies might focus on specific aspects such as sexual function, muscle mass and function, bone mineral status, or cognitive function, and/or can be some more general, composite measure of well-being or health status.

Well-controlled studies that have assessed the risks and benefits of androgen administration to elderly men are relatively few, in particular those with duration of 1 yr or longer and those having included substantial numbers of subjects. Not uncommon limitations of the studies that have been performed are a lack of clearly predefined principal efficiency criteria and heterogeneity as to the age and/or the initial androgen status of the study subjects. At present, there is probably no single controlled study that is of sufficient size and duration to allow for an evaluation of major clinical endpoints, such as fracture rates, long-term functionality and quality of life, long-term safety, or survival.

A point that deserves to be stressed before discussing the literature data in more detail is that it has now been clearly established that anabolic treatment effects can be obtained in initially eugonadal young and older men by administration of supraphysiological doses of androgens (425–427). Taken that we are presently not able to precisely define "physiological" androgen requirements for elderly men, observations of anabolic effects after androgen administration to elderly men with low normal or only moderately low testosterone cannot be taken as a *post hoc* proof that these men were initially androgen deficient. In other words, in the present state of the art it is not possible to make a clear distinction between "substitutive therapy" and "pharmaco-

TABLE 2. Summary of controlled trials (duration 3 wk to <3 months) in elderly men of therapies with increased exposure to (endogenous or exogenous) androgen

Study [first author, year (ref.)]	Study protocol Active treatment Duration No. of subjects	Main subject characteristics[a]	Main findings and remarks
Janowsky, 2000 (492)	Parallel groups T-enanthate im 150 mg/wk 1 month Act n = 10; PL n = 9	Community-dwelling (by advertisement) Age, 61–75 (mean 67) yr T "within age-specific reference" Baseline mean FT 1.2 ng/dl (ref: 1.6–4.3 ng/dl)	Improved working memory; no effect on mood state; no accurate guess of treatment assignment
Bakhshi, 2000 (480)	Parallel groups T-enanthate im 100 mg/2 wk ≤8 wk Act n = 9; PL n = 6	Admitted for revalidation in geriatric unit 65–90 yr No T limit Baseline T: ?	Functional Independence Measure (FIM = 18 item Lickert rating-scale) and handgrip strength improved *vs.* baseline only in Act group; Geriatric Depression Scale improvement Act >PL
Reddy, 2000 (496)	Parallel groups T-enanthate im 200 mg/2 wk 8 wk Act n = 14; PL n = 8	Healthy ≥ 65 (mean, 73) yr No T limit Baseline: T Act 408 ± 88 ng/dl; PL 289 ± 129 ng/dl	No effect on health-related quality of life (SF-36 questionnaire); significant difference in baseline T between Act and PL group
Cherrier, 2001 (493) and 2004 (528)	Parallel groups T-enanthate im 100 mg/wk 6 wk Act n = 13; PL n = 12	Community-dwelling (by flyers) 50–80 (mean, 67.5) yr No T limit Baseline T: 576 ± 180 ng/dl	Improved spatial memory (recall of walking route), spatial ability (block construction) and verbal memory (recall short story); improvement not evident for all measures
Amory, 2002 (479)	Parallel groups T-enanthate im 600 mg/wk (preoperatively) 4 wk Act n = 10; PL n = 12	Patients undergoing knee replacement surgery 58–86 (mean, 70) yr No T limit Baseline T 350 ± 130 ng/dl	Improved ability to stand at postsurgery d 3; nonsignificantly reduced hospital stay; increased hematocrit preoperatively (trend for higher postoperative hematocrit in treated subjects)
Liu, 2003 (467)	Crossover T-esters im Weekly injections: once 500 mg and twice 150 mg 3 wk n = 17	Healthy community-dwelling >60 (mean, 67.5) yr T ≤ 430 ng/dl at screening Mean baseline T > 430 ng/dl	Decreased total time slept; increased duration of hypoxemia and disrupted breathing during sleep; no change in driving ability, physical activity, mood, quality of life (SF-36), sleepiness or insulin sensitivity; decreased fat mass; increased BW and lean mass

All studies included are randomized, placebo-controlled, and double blind. Shown are only trials with at least 3-wk and less than 3-month duration of active treatment and specifically including older men (*i.e.*, with all men ≥50 yr old or mean age ≥60 yr) that have been published as full papers. Six trials were identified, including a total of 120 study subjects of whom 73 received active treatment. ref, Reference range; Act, active treatment; PL, placebo; n, number of subjects; BW, body weight; T, testosterone.

[a] Shown from top to bottom are: the type of subjects included, age, upper limit of serum T as inclusion criterion, and baseline T or FT.

logical treatment" because serum testosterone levels in the mid or upper physiological range for young men may very well be clearly supraphysiological for at least part of the study population of elderly men. Consequently, independently of the question whether such a treatment is useful, when administrating testosterone to elderly men with low normal or moderately low testosterone levels one cannot claim that this is a substitutive therapy that reestablishes a physiological situation. Moreover, several of the treatment regimens commonly applied as androgen replacement therapy result in androgen exposure that is at least transiently supraphysiological, also for young men. The latter is not only the case for intermittent im administration of testosterone esters, known to induce largely supraphysiological levels during the days immediately after the injection, but is also true when testosterone levels are continuously maintained in the upper range of the normal reference for young men (*e.g.*, with use of a testosterone gel), because such a treatment yield elevated mean testosterone levels compared with physiological conditions with lower serum levels during the afternoon and the first part of the night.

Although controlled data are for ethical reasons understandably scarce, endocrinologists would agree that androgen replacement is indicated anyhow in young hypogonadal men, and this is probably also the case for the rather limited fraction of elderly men that are clinically and biochemically frankly hypogonadal. On the other hand, if and when a favorable long-term ratio between benefits and risks is being established on the basis of clinically relevant endpoints, treatment of elderly men with androgens might very well be justifiable whether or not this constitutes a substitution therapy.

TABLE 3. Summary of controlled trials (duration 3 months to <1 yr) in elderly men of therapies with increased exposure to (endogenous or exogenous) androgen

Study [first author, year (ref.)]	Study protocol Active treatment Duration No. of subjects	Main subject characteristics[a]	Main findings and remarks
Nankin, 1986 (489)	Crossover T-cypionate im 200 mg/2 wk 12 wk n = 10	Ambulatory; referred for "impotence" Age, 54–71 yr T < 420 ng/dl Baseline T 320 ± 81 ng/dl; FT 10 ± 2.4 ng/dl (ref. 15–25)	Improved score for 5 questions on sexual activity treatment has helped? Sexual activity? Urge for sex? Enjoyment? Morning/sleep erection? 7 of 10 men improved libido
Tenover, 1992 (419)	Crossover T-enanthate im 100 mg/wk 3 months n = 13	Healthy community-dwelling (by advertisement) 57–76 yr Non-SHBG T < 46 ng/dl (ref. 46–121) Baseline T 334 ± 14 ng/dl; non-SHBG T 19 ± 3 ng/dl	Increased BW, lean mass; no change % body fat, body circumference, waist/hip ratio, handgrip strength or serum osteocalcin; decreased excretion hydroxyproline, decreased total-C, LDL-C; increased hematocrit
Janowsky, 1994 (495)	Parallel groups Transdermally, scrotal patch 15 ng 15 h/d 3 months Act n = 27; PL n = 29	Healthy men 60–75 (mean, 67) yr No T limit FT 1.6 ng/dl (ref: ?; "normal for age")	Improved spatial cognition (block design); no change verbal and visual memory, fine motor dexterity and speed, trail making test; mood. Treatment resulted in higher peak T levels but lower trough T levels and estradiol levels
Drinka, 1995 (507)	Parallel groups T-esters im 150 mg/70 kg BW/2 wk 6 months Act n = 8; PL n = 10	Long-term residents of nursing home 60–90 yr T < 320 ng/dl + FT < 1.2 ng/dl (ref: ?)	Two of 8 T-treated subjects developed erythrocytosis *vs.* none of 10 in PL group
Clague, 1999 (478)	Parallel groups T-enanthate im 200 mg/2 wk 12 wk Act n = 7; PL n = 7	Community-dwelling, healthy > 60 (mean, 68) yr T < 403 ng/dl Baseline T 325 ± 49 ng/dl	Increased BW, hemoglobin, red blood cell volume; no improvement strength handgrip, knee flexor or extensor, or leg extensor
English, 2000 (481) and Malkin, 2003 (482)	Parallel groups T transdermally (body patch) 5 mg/d 3 months Act n = 22; PL n = 24	CAD (chronic stable angina pectoris) 62 ± 2 yr No T limit Baseline T 390 ± 22 ng/dl Baseline FT 4.6 ± 0.2 ng/dl (ref. 0.7–13.9)	Increased time to 1 mm ST depression on ECG during treadmill test; improved score for pain perception and role limitation (SF-36); no change waist/hip ratio, BMI, or mean blood pressure
Ly, 2001 (470), 2002 (529)	Parallel groups DHT transdermally (gel) 70 mg/d 3 months Act n = 17; PL n = 18	Community-dwelling, healthy >60 (mean, 68) yr T < 432 ng/dl Baseline T 432 ± 89 ng/dl	Decreased skinfold thickness and fat mass; nonsignificant increase lean mass; no change waist/hip ratio; increased isokinetic force knee flexor dominant side; no change for 7 other measures muscle force knee and shoulder; increased hematocrit and hemoglobin; decrease total-C and LDL-C; no effect on gait, balance, mobility, cognition, or quality of life
Münzer, 2001 (312); Christmas, 2002 (460); Blackman, 2002 (471)	Parallel groups T-enanthate im 100 mg/2 wk 6 months Act n = 15 (to 21); PL n = 17	Community-dwelling, healthy (by mailing/advertisement) ≥65 (mean, 71) yr T ≤ 470 ng/dl (=1 SD below mean for young) Baseline T 440 ± 23 ng/dl	Trend for decreased abdominal sc fat; no change waist/hip ratio, abdominal area, or visceral fat; nonsignificant increase lean mass; no effect muscle strength, markers bone turnover, BMD hip, lumbar spine, total body or radius
Kunelius, 2002 (491)	Parallel groups DHT transdermally (gel) 125 mg/d initial 30 d, thereafter 125 to 250 mg/d according to DHT level on d 20 6 months Act n = 60; PL n = 60	NPT ≤1/wk + at least one other "andropause" symptom 50–70 (mean, 58) yr T ≤ 432 ng/dl or SHBG >30 nmol/liter Baseline T 493 ± 152 ng/dl	Significant improvement at 6 months for score for a question on the ability to maintain erections and at 3 months for morning erections (out of 12 questions on sexual function); no effect on mood, libido, well-being, or vitality

B. Clinical trials with intervention to increase androgen exposure

There have been several recent reviews of and commentaries on treatment of middle-aged and elderly men with androgens (428–438), including two extensive systematic reviews of clinical trials (428, 432). Tables 2–4 summarize the essentials for selected reports of controlled clinical trials with active treatment intended to increase androgen exposure in elderly men either by androgen administration or by stimulation of endogenous testosterone production; clinical trials

TABLE 3. Continued

Study [first author, year (ref.)]	Study protocol Active treatment Duration No. of subjects	Main subject characteristics[a]	Main findings and remarks
Lambert, 2003 (530), 2002 (531)	Parallel groups MA po 800 mg/d +/− (RT) +/− T-enanthate im 100 mg/wk MA+T n = 8; MA+PL n = 7; MA+T+RT n = 7; MA+PL+RT n = 6	Healthy 60–85 (mean, 67) yr No T-limit Mean baseline T around 430–500 ng/dl	T treatment compared to PL reduced total body fat mass and thigh fat cross-sectional area; no effect on muscle mass or strength or total-C/HDL-C ratio
Ferrando, 2002 (472), 2003 (532)	Parallel groups T-enanthate im 4 times weekly, then every 2 wk 50–400 mg (variable dose to maintain nadir serum T ≥ 490 and ≤ 807 ng/dl) 24 wk Act n = 7; PL n = 5	Healthy ≥60 (mean, 67) yr T ≤ 480 ng/dl Baseline T 279–458 ng/dl	Decreased % body fat; increased protein balance, total and leg lean mass, muscle volume, leg and arm muscle strength (all strength scores improved; no improvement endurance)
Liu, 2002 (473), 2003 (485)	Parallel groups Recombinant hCG sc 250 μg (5000 IU)/biweekly 3 months Act n = 20; PL n = 20	Community-dwelling, healthy >60 (mean, 67.5) yr T ≤ 432 ng/dl Baseline T 320 ± 12 ng/dl; FT 5 ± 0.1 ng/dl	Increased BW, lean mass; decreased fat mass; nonsignificant increase muscle strength knee and shoulder; no change physical activity, sexual function, balance; no change brachial artery size, vascular function or pressure; decreased total-C, LDL-C and triglycerides; no change HDL-C
Schroeder, 2003 (474)	Parallel groups Oxymetholone po 50 or 100 mg/d 12 wk Act 50 mg n = 11; Act 100 mg n = 9; PL n = 11	Community-dwelling 65–80 (mean, 71) yr No T limit Baseline T 360–382 ng/dl	Decreased fat mass; increased BW, total and upper extremity lean mass, muscle strength (chest press); nonsignificant increase leg press strength; no change insulin sensitivity, total-C, LDL-C, triglycerides; decreased HDL-C
Malkin, 2003 (482)	Parallel groups T-esters im 100 mg/2 wk 12 wk Act n = 10; PL n = 10	Congestive heart failure 62 ± 3 yr No T limit Baseline T 455 ± 70 ng/dl	Reduced QT dispersion on ECG (QT dispersion = difference between maximum and minimum QT across all 12 leads)
Kenny, 2004 (494)	Parallel groups T-enanthate 200 mg/3 wk 12 wk Act n = 6; PL n = 5	Mild to moderate cognitive impairment 73–87 (mean, 80) yr BioT < 128 ng/dl Baseline T 410 ± 112 ng/dl; bioT 92 ± 42 ng/dl	No changes in behavior, function, cognitive performance, or score for the geriatric depression scale
Dougherty, 2005 (487); Leder, 2004 (490)	Parallel groups Aromatase inhibitor anastrozole po 1 mg/d or biweekly 12 wk Act daily n = 12; Act biweekly n = 11; PL (daily) n = 14	Generally healthy (by advertisement) 62–74 (mean, 67) yr 150 ≤ T ≤ 350 ng/dl Baseline T group means: 274 ± 51 to 290 ± 50 ng/dl BioT group means, 99 ± 31 to 115 ± 37 ng/dl	No effect on health-related quality of life (SF-36), on International Index of Erectile Function, or on American Urological Association Symptom Index Score; no changes inflammatory parameters, insulin sensitivity, triglycerides, total-C, LDL-C; significant decrease HDL-C in 2 × 1 mg/wk only (no significant between group differences); no change hematocrit or hemoglobin; increase PSA
Schroeder, 2004 (475 and 476)	Parallel groups Oxandrolone po 2 × 10 mg/d 12 wk Act n = 20; PL n = 12	Community-dwelling ≥60 (mean, 72) yr No T limit Baseline T Act, 369 ± 147 ng/dl; PL, 357 ± 153 ng/dl	Increase lean mass; increase *vs.* placebo of leg and chest press strength; reduced total and trunk fat by DXA; decreased visceral adipose tissue (VAT), sc abdominal adipose tissue (SAT), VAT over SAT ratio, and thigh sc fat by MRI; increased insulin sensitivity; decreased HDL-C, increased LDL-C, no change prostate symptomatology or hematocrit; decrease PSA, serum alkaline phosphatase; increase liver transaminase (ALT; AST)

All studies included are randomized, placebo-controlled, and double blind. Shown are only trials with at least 3 months and less than 1-yr duration of active treatment and specifically including older men (*i.e.*, with all men ≥ 50 yr old or mean age ≥ 60 yr) that have been published as full papers. Seventeen trials were identified, including a total of 561 study subjects of whom 306 received active treatment. ref, Reference range; Act, active treatment; PL, placebo; po, orally; n, number of subjects; BW, body weight; T, testosterone; bioT, bioavailable (non-SHBG-bound) testosterone; total-C, total cholesterol; MA, megestrol acetate; RT, resistance physical training; DXA, dual-energy x-ray absorptiometry.

[a] Shown from top to bottom are: the type of subjects included, age, upper limit of serum T, FT, or bioT as inclusion criterion, baseline T, FT, or bioT.

TABLE 4. Summary of controlled trials (duration 12–36 months) in elderly men of therapies with increased exposure to (endogenous or exogenous) androgen

Study [first author, year (ref.)]	Study protocol Active treatment duration No. of subjects	Main subject characteristics[a]	Main findings and remarks
Reid, 1996 (439)	Crossover open label! T-esters im 250 mg/month 12 months n = 15	Asthmatic men on long-term glucocorticoid treatment Age, 61 ± 11 yr No T limit Baseline T 325 ± 40 ng/dl	Increased lumbar spine BMD; nonsignificant increase hip and total body BMD; decreased hydroxyproline excretion and serum bone alkaline phosphatase, fat mass; increased lean mass
Sih, 1997 (458)	Parallel groups T-cypionate im 200 mg im/2 wk 12 months Act n = 17; PL n = 15 (dropouts, Act n = 7; PL n = 3)	Community-dwelling, healthy ≥50 (mean, 65) yr BioT ≤ 60 ng/dl (ref. 70–250) Baseline T 294 ± 26 ng/dl; BioT 42 ± 5 ng/dl	Increased bilateral handgrip strength, no significant change fat mass, BMI, waist/hip ratio, serum osteocalcin, alkaline phosphatase, PSA; increased hematocrit and hemoglobin; no effect on cognition or depression
Snyder, 1999 (461 and 468); 2001 (483)	Parallel groups T transdermally (scrotal patch) 6 mg/d (+ calcium and vitamin D) 36 months Act n = 54; PL n = 54 (dropouts, Act n = 4; PL n = 8)	Community-dwelling, healthy (advertisement; mailing) >65 (mean, 73) yr T < 475 ng/dl (*i.e.*, 1 SD below mean for young men) Lumbar spine BMD below mean for healthy young men Baseline T 367 ± 79 ng/dl	Increase lumbar spine BMD not significant *vs.* PL (negative correlation % change BMD *vs.* basal T); no change hip BMD, markers bone turnover; decreased fat mass; increased lean mass, hematocrit, hemoglobin, PSA; no change BW, BMI, muscle strength; no change energy, sexual function, lipoprotein profile, respiratory distress index, urinary flow; less decline perception of physical functioning (*i.e.*, 1 of 8 scores SF-36)
Kenny, 2001 (462); 2002 (484 and 486)	Parallel groups T transdermally (body patch) 5 mg/d (+ calcium and vit D) 12 months Act n = 34; PL n = 33 (dropouts, Act n = 10; PL n = 13)	Community-dwelling (mailings, flyers, lectures) 65–87 (mean, 76) yr BioT < 128 ng/dl (ref. 128–429) Baseline T 388 ± 173 ng/dl; bioT 92 ± 34 ng/dl	Prevented decrease BMD femoral neck compared to PL; no significant effect for BMD lumbar spine, hip trochanter or whole body; no change markers bone turnover; decreased fat mass, trend increase lean mass, no effect muscle strength, total-C, LDL-C, triglycerides, brachial artery vascular function; no effect cognition, health perception (SF-36), hematocrit, hemoglobin, PSA
Wittert, 2003 (477)	Parallel groups T-undecanoate po 2 × 80 mg/d 12 months Act n = 39; PL n = 37 (dropouts, Act n = 4; PL n = 5)	Community-dwelling, healthy (advertisement) 60–86 (mean, 69) yr FAI (*i.e.*, T/SHBG) ≥ 0.3 to ≤ 0.5 (ref. young normal: >0.5) ≥2 symptoms on ADAM questionnaire Baseline T 490 ± 130 ng/dl	Decreased fat mass; increased lean mass; no change handgrip, quadriceps, or calf strength; no change BW, LDL-C, triglycerides; decreased HDL-C, increased hematocrit; no change blood pressure, PSA
Crawford, 2003 (463)	Parallel groups T-esters or NAN im 200 mg/2 wk (+ calcium PO) 12 months Act T n = 18; Act NAN n = 17; PL n = 16 (dropout Act T n = 4; Act NAN n = 7; PL n = 3)	Long-term glucocorticoid therapy 60.3 ± 1.9 yr Baseline T 400 ± 14 ng/dl	Increased muscle mass and strength with decreased fat mass (both T and NAN); increased lumbar spine BMD (only T); no effect hip and total body BMD, markers bone turnover; improved overall quality of life (only T) (Qualeffo-41 dedicated questionnaire for osteoporosis patients)
Amory, 2004 (459); Page, 2005 (469)	Parallel groups T-enanthate im 200 mg/2 wk +/− 5 mg FIN po T dose adjusted if hematocrit >52%: mean actual dose/2 wk: 158 ± 36 (T); 164 ± 40 T + FIN 36 months Act T n = 24; Act T + FIN n = 22; PL n = 24 (dropouts, Act T n = 7; Act T + FIN n = 7; PL n = 6)	Community-dwelling, healthy (mailings, advertisement) 65–83 (mean, 71) yr T < 350 ng/dl Baseline T 283 ± 49 ng/dl	Increased lumbar spine and hip BMD (T and T + FIN); decreased serum bone-specific alkaline phosphates and urinary deoxypyrridinolines; no effect on serum osteocalcin; increased hematocrit (T and T + FIN), PSA (only T); increased prostate volume T > T + FIN; improved performance in timed functional test, increased lean mass and handgrip strength and decreased fat mass and waist/hip ratio (T and T + FIN); no improvement low leg strength (T and T + FIN); decreases in serum leptin, total-C, LDL-C and triglycerides; unchanged HDL-C

All included studies are randomized, placebo-controlled, and double-blind (unless indicated otherwise). Shown are only trials with at least 1-yr duration of active treatment and specifically including older men (*i.e.*, with all men ≥ 50 yr old or mean age ≥ 60 yr) that have been published as full papers. Seven trials were identified, including a total of 419 study subjects of whom 240 received active treatment. ref, Reference range; Act, active treatment; PL, placebo; vit, vitamin; po, orally; n, number of subjects; BW, body weight; T, testosterone; bioT, bioavailable (non-SHBG-bound) testosterone; total-C, total cholesterol; FIN, finasteride; NAN, nandrolone-decanoate.

[a] Shown from top to bottom are: the type of subjects included, age, upper limit of serum T, FT or bioT as inclusion criterion, and baseline T, FT or bioT.

with administration of DHEA are discussed separately in *Section V.D*. We have included only those trials that were randomized, that have addressed endpoints of clinical relevancy, and that have included specifically (or allowed to analyze separately) elderly men. As to the latter, the arbitrary criterion for inclusion of the study was that all men in the study were at least 50 yr old or that the mean age was at least 60 yr. Unless otherwise specified (439), all trials were placebo-controlled and double-blinded. Arbitrarily, we have considered only trials with at least 3-wk duration of the active treatment period.

A systematic search resulted in the identification of six such trials with duration of active treatment from at least 3 wk to less than 3 months, having included a total of 120 men of whom 73 received active treatment (Table 2); identification of 17 trials with at least 3 months to less than 12 months of active treatment, having included a total of 561 men of whom 306 were on active medication (Table 3); and identification of seven trials with 1- to 3-yr duration of active treatment and a total of 419 participants, of whom 240 received active medication (Table 4). Thus, in these 28 considered trials, a total of 576 elderly men have received active androgenic treatment of 3-wk to 36-month duration under controlled conditions. There is great heterogeneity as to the type of treatment, the characteristics of the study subjects, the considered endpoints, and the initial androgen status of the men. As to the latter, a substantial proportion of the men included in these studies did not have biochemically documented hypogonadism at baseline. Reasons for noninclusion of trials in this summary were lack of direct clinical implications (*e.g.*, Refs. 308, 440, and 441), availability of the data only in abstract form, inclusion of a substantial proportion of younger men (*e.g.*, Refs. 224, 369, and 442–447), nonrandomized study design, or related methodological issues interfering with the evaluation of androgen treatment effects (*e.g.*, Refs. 440, 441, 445, and 447–457).

1. Skeletal effects

a. Bone turnover. The observed effects of treatment on biochemical markers of bone turnover have been inconsistent. In response to im injection of testosterone esters, Tenover (419) observed an increase of serum osteocalcin with decreased urinary excretion of hydroxyproline in a small crossover study in 13 men with initially low bioT, and Sih *et al.* (458) found an increase of serum osteocalcin and alkaline phosphatase in 10 men compared with 12 placebo-treated subjects, whereas Amory *et al.* (459) observed no effect on serum osteocalcin but a decrease of serum bone-specific alkaline phosphatase and urinary deoxypyridinoline after 6 months of treatment in 24 men compared with 22 placebo-treated subjects, and Reid *et al.* (439) described a decrease of both serum bone specific alkaline phosphatase and urinary excretion of hydroxyproline in a crossover study in 15 glucocorticoid-treated elderly men. On the other hand, testosterone-ester injections (n = 19) had no significant effect *vs.* placebo (n = 17) in a study by Christmas *et al.* (460), and no significant treatment effect compared with placebo-treated controls was observed by Snyder *et al.* (461) in 50 men treated during 3 yr with testosterone by scrotal patch, by Kenny *et al.* (462) in 24 men receiving testosterone by transdermal route for 1 yr with body patches, or by Crawford *et al.* (463) in long-term glucocorticoid-treated elderly men during 1-yr treatment with injections of either testosterone-esters (n = 14) or nandrolone-ester (n = 10). These overall largely negative findings might reflect the facts that age-related changes of the markers of bone turnover in untreated healthy elderly men are only limited anyhow (292), that the men in both the active and the placebo treatment groups have received calcium and vitamin D supplements, and that testosterone treatment exerts complex androgenic and estrogenic influences on bone metabolism (62, 294).

b. BMD. As to the effects on BMD, the findings are also rather mixed. In the study by Christmas *et al.* (460), 100 mg testosterone enanthate im every 2 wk was without effect on BMD at any skeletal site in community-dwelling elderly men with normal serum testosterone, but the study is inconclusive considering the small number of subjects and the treatment duration of only 6 months. In the study by Snyder *et al.* (461) in elderly men with low normal or moderately low serum testosterone, lumbar spine BMD increased in both the placebo group (n = 46) and the testosterone-treated group (n = 50), both receiving calcium and vitamin D supplements, without significant treatment effect *vs.* placebo over the 3-yr duration of the treatment; there were no significant effects for hip BMD. Interestingly, in the testosterone-treated men, BMD response at the lumbar spine was inversely correlated to the baseline serum testosterone levels, a significant treatment effect being observed only in the study subjects with initially low serum testosterone, *i.e.*, with a pretreatment serum testosterone between 100 and 300 ng/dl (Fig. 7). Kenny *et al.* (462) observed a maintained femoral neck BMD during 1-yr testosterone administration to elderly men with initially moderately low bioT compared with a small significant decrease in the placebo group, resulting in an overall positive treatment effect of 1.9%, both treatment arms receiving calcium and vitamin D supplementation; there was no treatment effect for BMD at the hip trochanter, at the lumbar spine, or for the whole skeleton. In elderly men selected on the basis of low pretreatment serum testosterone but not of a prevalent low BMD, during 3 yr of treatment with 200 mg testosterone enanthate im every 2 wk either alone (n = 17) or in combination with daily oral administration of 5 mg finasteride (n = 15), a 5α-reductase inhibitor, Amory *et al.* (459) observed a significant progressive increase of BMD at the lumbar spine and at the total hip region, but not at the femoral neck, compared with unchanged BMD values in the placebo-treated controls, no calcium or vitamin D supplements being provided. In this study, the observed treatment effects were positively correlated with the magnitude of increase of serum levels of both testosterone and estradiol, but not with baseline hormone levels. Finally, in elderly men under chronic systemic treatment with glucocorticoids, Crawford *et al.* (463) observed that 12-month treatment with testosterone-esters (n = 14) resulted in an increase of lumbar spine BMD of 4.0% *vs.* placebo-treated subjects (n = 13) without significant effect at the femoral neck or for the total skeleton, whereas treatment with the minimally aromatizable androgenic compound nandrolone (n = 10) failed to significantly affect BMD at any of the measurement sites.

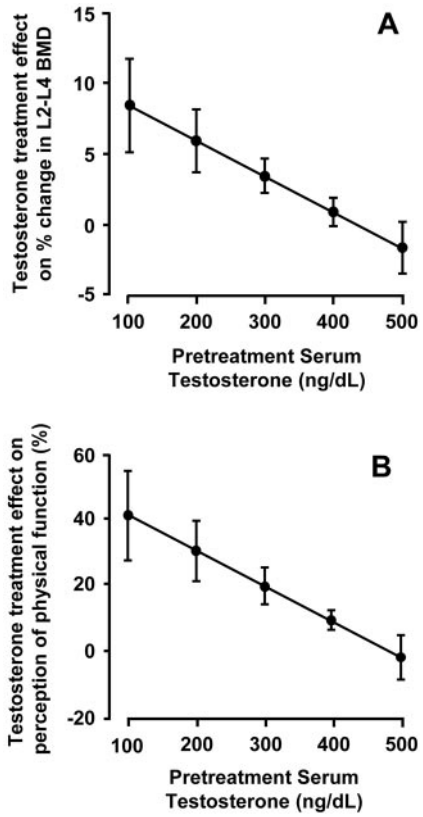

FIG. 7. Testosterone treatment effect on percentage change in BMD (A) and score for perception of physical function (B) determined by the MOS SF-36 questionnaire as a function of pretreatment serum testosterone concentration in men over 65 yr of age. The lower the pretreatment serum testosterone levels, the greater the testosterone treatment effect; $P < 0.001$ for testosterone treatment effect for both considered endpoints. To convert testosterone to nanomoles per liter, multiply by 0.0347. [Adapted from P. J. Snyder *et al.*: *J Clin Endocrinol Metab* 84:1966, 1999 (461), and 84:2647, 1999 (468) with permission from The Endocrine Society.]

Previously, Reid *et al.* (439) observed in elderly men under chronic glucocorticoid administration a positive treatment effect of 5% compared with controls for lumbar spine BMD after 1 yr of treatment with testosterone esters; for BMD at the femoral neck and hip trochanter, the treatment effect amounted to 0.3 and 2.7%, respectively.

c. Fractures. Data on effects of androgen administration to elderly men on fracture rates are not available.

In conclusion, the data do not indicate a beneficial skeletal effect of testosterone administration to elderly men with normal or borderline serum testosterone. But, in agreement with the findings of the observational studies suggesting that declining sex steroid levels may adversely affect the maintenance of bone mass in the elderly, the intervention studies do indicate favorable effects of treatment on BMD in those men with pretreatment serum testosterone clearly below the range for young men, as well as the possibility of favorable effects on BMD in elderly men under chronic treatment with glucocorticoids.

The observations of positive effects of testosterone on BMD when used in combination with a 5α-reductase inhibitor (459) and of relative inefficacy compared with testosterone of a nonaromatizable androgen (463) tend to support the suggestion from the observational studies that aromatization is important for full expression of beneficial testosterone effects on bone in elderly men and thus that, as far as the skeletal effects are concerned, use of testosterone is the most physiological approach to androgen treatment in elderly hypogonadal men. Alternative compounds may not ensure adequate skeletal protection even if they are aromatizable as suggested by data in young hypogonadal men treated with the more potent androgen 7α-methyl-19-nortestosterone (464), because at the dosages usually administrated the estrogenic metabolites are not able to maintain BMD.

Although the data do support the view that favorable effects on BMD are a benefit of testosterone administration to elderly men who are hypogonadal or to glucocorticoid-treated elderly men, the clinical relevancy in terms of reduced fracture risk remains to be established. With the information presently available, increase of bone mass or prevention of fractures should not as such be regarded as indications for testosterone administration to elderly men. In this context, it can be noted that in the study showing the most convincing treatment effects of testosterone in elderly men (459) these men not only had low initial serum testosterone levels but also did not receive calcium or vitamin D supplementation. Moreover, for oral alendronate (465) and for daily sc injections of recombinant (1–34)PTH (466), two drugs presently available for treatment of men with low BMD, it has been documented that, combined with calcium and vitamin D supplements, these drugs have beneficial effects on BMD independent of age and androgen status of the patients.

2. Effects on body composition

a. Lean and fat mass. In trials on androgen administration to elderly men, the effects on body composition and muscle strength have been the most extensively studied efficacy criteria. Studies of 3-wk (467) to 3-yr (468, 469) duration have consistently indicated that androgen administration to elderly men tends to decrease fat mass and increase lean mass.

Using the hydrostatic weighing technique, Tenover (419) observed a 1.8-kg increase of lean body mass in elderly men with low initial bioT after 3 months of weekly injections of 100 mg testosterone enanthate compared with placebo, without significant change in percentage body fat or in waist to hip body circumference ratio. In the study by Liu *et al.* (467), short-term administration of largely supraphysiological doses of 800 mg testosterone esters over a 3-wk period induced a 3-kg increase of apparent lean body mass and a 1-kg decrease of fat mass as estimated by bioelectrical impedance measurements. Administration of 70 mg DHT daily by transdermal route for 3 months in men with borderline low serum testosterone (470) resulted in reduced skin fold thickness and in a decrease of total body fat by about 2 kg with nonsignificant increase of body lean mass as assessed by bioelectrical impedance; there was no change in waist to hip ratio. After 6 months of administration of 100 mg testosterone enanthate every 2 wk to elderly men with normal baseline serum testosterone (471), there was a nonsignificant 1.4-kg increase of total lean mass and a 1.2-kg decrease of fat mass assessed by dual-energy x-ray absorptiometry (DEXA) with

a reduction by 7% of abdominal sc fat without change in total abdominal area or visceral fat as assessed by magnetic resonance imaging (MRI) and no change in waist to hip ratio. Ferrando *et al.* (472) treated elderly men with normal to borderline low testosterone levels for 6 months according to a flexible treatment regimen with testosterone enanthate aimed at maintaining testosterone within the upper physiological range for young men, which in reality undoubtedly resulted in supraphysiological mean testosterone levels in most study subjects, and observed a substantial 6.2-kg mean gain of total lean mass and 4% decrease of fat mass relative to placebo treatment as assessed by DEXA. Liu *et al.* (473) stimulated endogenous testosterone production by biweekly injections of recombinant hCG in elderly men with borderline low serum testosterone and observed after 3 months a modest but significant decrease of fat mass and increase of lean mass measured by bioelectrical impedance. Schroeder *et al.* (474), on the other hand, obtained substantial 3.3- and 4.2-kg increases of total lean mass in healthy elderly men treated for 12 wk with a daily oral dose of 50 or 100 mg of the 17-methylated androgen oxymetholone, respectively, which was accompanied by a 2.6- and 2.5-kg decrease of fat mass as estimated by DEXA. In a study with daily oral administration of 20 mg of the 17-methylated androgen oxandrolone for 12 wk (475, 476), total lean mass increased by a mean of 3.0 kg and total fat mass decreased by 1.9 kg as assessed by DEXA; the changes in fat mass but not in lean mass were still different from baseline 12 wk after treatment discontinuation.

As to studies of longer duration, Sih *et al.* (458) in a small-scaled study found no change in percentage body fat by bioelectrical impedance, but there was a significant reduction in serum leptin levels during 1-yr treatment with 200 mg testosterone cypionate every 2 wk (n = 10) compared with placebo treatment (n = 12), whereas Kenny *et al.* (462) observed by DEXA at the end of 12 months of treatment with transdermal testosterone (n = 24) in men with moderately low bioT a mean decrease of 1.7% of fat mass and a 1-kg increase of lean mass, only the former being significantly different from changes under placebo (n = 20). In the study by Wittert *et al.* (477) in elderly men with low FAI receiving an oral daily dose of 160 mg testosterone undecanoate for 1 yr (n = 35), there was a mean treatment gain of 1.7 kg lean body mass by DEXA compared with the placebo group (n = 32), with a mean decrease of fat mass by 1.1% compared with an increase of 4.6% in the placebo-treated subjects. Snyder *et al.* (468) assessed by DEXA changes in body composition over 36 months in elderly men with normal or low serum testosterone treated with testosterone by scrotal patches (n = 50) and observed a 1.7-kg positive difference in mean treatment effects compared with placebo (n = 46) for lean mass, whereas there was a 2.3-kg negative mean difference for fat mass. After 36 months of treatment of men with moderately low bioT with 200 mg testosterone enanthate im every 2 wk alone (n = 17) or combined with 5 mg oral finasteride daily (n = 15), Page *et al.* (469) observed a mean 3.7-kg increase of lean mass as assessed by DEXA with no changes in the placebo group (n = 18); testosterone treatment with or without finasteride resulted in a mean decrease of fat mass with 5.5 and 6.3%, respectively.

In glucocorticoid-treated elderly men (n = 15), Reid *et al.* (439) observed a 0.9-kg upward trend in lean body mass during a 12-month treatment with testosterone esters compared with a 1.4-kg decrease during the control period and a 0.8-kg downward trend of fat mass compared with a 2.1-kg increase in the control period. Again in glucocorticoid-treated men, Crawford *et al.* (463) observed that both testosterone and nandrolone esters increased lean body mass by 1.8 and 2.8 kg, respectively, compared with a 0.5-kg decrease in the placebo group.

b. Functional correlates. The picture is less consistent when considering the body composition-related functional changes under androgen treatment. Tenover (419) observed no effect of treatment on hand grip strength, and Clague *et al.* (478) in their small-scaled study also found no significant improvement of hand grip or leg strength. Ly *et al.* (470) observed a positive effect of transdermal DHT treatment on peak torque developed during isokinetic dynamometry for dominant knee flexion, but there was no significant treatment effect for seven other measures of isokinetic contraction at knee and shoulder; there was also no change in gait, balance, or the results for mobility tests. Blackman *et al.* (471) found no effect of testosterone administration on either a total body strength assessment based on four upper body and two lower body strength measures or on maximum aerobic capacity. In the study by Liu *et al.* (473), increase of endogenous testosterone levels during treatment with hCG failed to significantly affect shoulder and knee strength, physical activity, gait, or balance. Oral administration of 160 mg testosterone undecanoate daily failed to significantly affect hand grip, quadriceps or calf strength compared with placebo in the study of Wittert *et al.* (477), however the authors did note for the treatment group a significant positive association between augmentation of lean body mass and increase of quadriceps strength. No effect on leg extension strength in men treated for 1 yr with testosterone body patches was observed compared with the changes under placebo in the study of Kenny *et al.* (462), and, similarly, 3-yr testosterone administration by scrotal patches increased lean mass mainly in the trunk rather than in the limbs and failed to improve relative to placebo the hand grip, knee flexion, or knee extension strength as reported by Snyder *et al.* (468).

There were also positive reports, however. In the study by Ferrando *et al.* (472), the increase of total lean mass, induced by a relatively high testosterone dose, was accompanied by increase of muscle protein synthesis, leg lean mass, and muscle volume and by increased muscle strength for all performed arm and leg measurements. Schroeder *et al.* (474) in a study with oxymetholone observed a dose-dependent increase of chest press and lateral pull-down strength, positively associated with changes in upper limb lean body mass, but there was only a nonsignificant trend for improved leg strength. In a study with oxandrolone (476), there was after 12 wk an increased strength for leg flexion, leg press, and chest press with no residual treatment effect 12 wk after discontinuation of treatment. Sih *et al.* (458) observed an increase of grip strength after 3 months of testosterone injections, which was maintained during the 1-yr total duration of the treatment. In glucocorticoid-treated elderly men,

Crawford *et al.* (463) noted that both testosterone and nandrolone esters improved knee muscle strength. Amory *et al.* (479) reported that short-term high-dose administration of 600 mg testosterone enanthate weekly to elderly men in preparation of knee replacement surgery resulted in an improved ability to stand on postsurgery d 3 and nonsignificantly shortened hospital stay, whereas Bakhshi *et al.* (480) described an improvement of hand grip strength and of the Functional Independence Measure in testosterone-treated geriatric patients admitted for revalidation. In men with moderately low baseline testosterone levels, Page *et al.* (469) observed that testosterone injections, with or without finasteride, improved performance in a timed functional test as well as handgrip strength. These effects, parallel to the increases in lean mass, were significant at 6 months (first follow-up measurement) and maintained for the rest of the 36 months of treatment; there were, however, no effects of treatment on isokinetic lower extremity strength measured at both ankle and knee.

In summary, overall the trials indicate that interventions resulting in augmented androgen exposure increase lean body mass and reduce body fat mass in elderly men similarly to what has been reported for younger men (426) and in agreement with the observations of Bhasin *et al.* (427) that older men are as responsive as young men to the anabolic effects of testosterone on skeletal muscles. With commonly used androgen dosages, the amplitude of the effects is rather modest; the effects are usually evident within the first months of treatment and plateau thereafter. Unfortunately, these clear-cut findings for body composition have so far not been matched by a similarly convincing demonstration of functional clinical benefits. A majority of available studies failed to demonstrate improved muscle strength, in particular in the legs, and there is presently no convincing documentation of immediate clinical benefits such as improved mobility or functional autonomy or reduced risk of falls. There is, *a fortiori*, no documentation of beneficial functional effects above what might be achieved with nonpharmacological intervention such as exercise programs. Still, some studies did reveal improved muscle strength, albeit this may require administration of supraphysiological androgen doses, and it has been suggested that failure to demonstrate beneficial effects of androgen treatment on functionality might to a large extent be due to the use of inappropriate methodology (433). Furthermore, the few available reports pertaining to elderly men that are frail or at risk of frailty, such as those under chronic treatment with glucocorticoids and those admitted for revalidation or for major surgery, did yield encouraging findings that seem to warrant investigation of potential applications of anabolic androgen treatment in elderly men in clinical trials that should be adequately powered, should include well-defined patient groups, and should assess predefined and clinically relevant efficacy and safety criteria. In the present state of the art, improved body composition should be viewed as a potential benefit of androgen treatment to elderly men with hypogonadism, but the anabolic effects should not *per se* be considered an indication for androgen administration to elderly men.

3. Atherosclerosis and CAD. Few studies focused specifically on cardiovascular efficacy criteria. English *et al.* (481) reported that 3-month administration of testosterone by transdermal route to men with CAD (n = 22) improved the time to ST-segment depression on electrocardiogram (ECG) during exercise compared with placebo-treated patients, the testosterone-treated men having also a better score for self-perceived pain and role limitation resulting from physical problems in the Short Form 36 quality-of-life questionnaire. The same group described how testosterone treatment reduced the difference between maximum and minimum QT across the 12 leads of an ECG, *i.e.*, the QT-segment dispersion, a measure of impaired conduction and repolarization in elderly men with congestive heart failure (482). However, there is no study in the elderly that was powered for assessment of hard cardiovascular clinical endpoints. In the study of 3-yr duration by Snyder *et al.* (483), clinically manifest cardiovascular events were reported for nine of 54 men in the testosterone group compared with five of 54 in the placebo-treated men (relative risk, 1.8; 95% confidence interval, 0.7–5.0); in the 3-yr study by Amory *et al.* (459), a case of cerebral hemorrhage in one of the testosterone-treated men was the only reported severe cardiovascular adverse event for all treatment groups.

In many of the studies on androgen administration to elderly men, variables associated with cardiovascular risk have been measured, and the findings have generally been rather neutral. In elderly men with low normal to moderately low initial serum testosterone levels, neither increase of endogenous testosterone by injections of recombinant hCG (473) nor transdermal testosterone administration (484) resulted in significant alterations of brachial artery vascular reactivity, and for none of the treatment studies in elderly men were treatment-related changes in blood pressure reported. Many studies assessed some parameter of regional fat distribution, but they failed to observe relevant treatment effects. In none of the several studies assessing the waist circumference and/or the waist to hip circumference ratio was there a significant reduction (312, 458, 463, 470, 481, 485); in the study by Snyder *et al.* (468), the decrease of fat mass was not significant for trunk fat as assessed by DEXA; in the study by Münzer *et al.* (312), testosterone treatment failed to affect abdominal area and visceral fat as assessed by MRI. A decrease of trunk fat was observed under treatment of elderly men with oral synthetic androgens (474, 475). Page *et al*. (469) observed a decrease of trunk fat during testosterone treatment, however, accompanied by an increase of the waist over hip circumference ratio.

As to the blood lipid profile, some studies observed no changes when assessing total cholesterol, LDL-C, HDL-C, and/or triglycerides (458, 463, 472, 478, 483), apolipoprotein A1 or B, or lipoprotein (a) (483); several studies revealed unchanged levels for total cholesterol, LDL-C, and triglycerides with decreased values for HDL-C (439, 474, 477, 486, 487) or a decreased HDL-C with increased LDL-C (475), whereas in other studies there was a decrease of total cholesterol and LDL-C with unchanged HDL-C (419, 474, 477, 484). In no study was an increase in HDL-C reported, in apparent contrast with reports of positive associations of serum testosterone and HDL-C in epidemiological studies

(333–335, 337). No treatment effect on insulin sensitivity was observed in the study of Liu *et al.* (485) with stimulation of endogenous testosterone production by administration of hCG, in a study by Dougherty *et al.* (487) with stimulation of testosterone production with an aromatase inhibitor, or in the study of Schroeder *et al.* (474) with use of the androgenic compound oxymetholone. Insulin sensitivity was reported to be improved under oral treatment with 20 mg oxandrolone daily (475).

In conclusion, although in observational studies moderately low serum testosterone levels as seen in aging men are associated with an increased risk of atherosclerosis and CAD (see *Section III.C.3*), there is presently no evidence that androgen administration to elderly men may prevent the occurrence or improve the outcome of cardiovascular diseases. Treatment with moderate doses of testosterone appears to have rather neutral or mixed effects on cardiovascular risk factors in elderly men.

4. Sexual function. Whereas several studies that have indicated that androgen treatment improves sexual function of hypogonadal men have included some older patients (369, 420, 443, 445, 488), information from controlled trials specifically on sexual function in the elderly remains scarce. In a small double-blind study with crossover design in 10 aging men with erectile dysfunction of at least 6-month duration and moderately low serum testosterone levels, administration of 200 mg testosterone cypionate im every 2 wk for 12 wk significantly improved the patients' perception of sexual function compared with placebo treatment (489). In the study by Snyder *et al.* (468), 3-yr testosterone administration by scrotal patch to elderly men with normal or moderately low serum testosterone was without effect on an average score for four questions on sexual function. Similarly, in elderly men with borderline low testosterone levels, Liu *et al.* (473) observed no treatment effect of stimulated testosterone secretion by recombinant hCG administration for 3 months on the patients' perception of sexual activity. Also, stimulation of endogenous testosterone secretion by administration of an aromatase inhibitor was without measured effect on sexual function in men with moderately low pretreatment serum testosterone (490). In older men with low frequency of NPT and normal baseline serum testosterone, Kunelius *et al.* (491) observed that 6 months of treatment with DHT gel compared with placebo was without effect on libido and improved a score for early morning erection only during the first 3 months of treatment, whereas there was an improved score over the 6 months of DHT administration for ability to maintain erection during intercourse.

These limited and disparate findings do not constitute adequate clinical documentation to support the use of androgen treatment with the specific aim to improve sexual function in elderly men. Many of the aforementioned studies have used rather crude instruments to evaluate (the perception of) sexual function so that additional studies are needed to allow for conclusions on the effects of androgen administration on sexual function in elderly men. Nevertheless, whereas the design of the more numerous trials that have included hypogonadal men in a broader age range does not allow for confirmation of the efficacy of androgen treatment on sexual function specifically in the subgroup of older study subjects, it can be noted that they provided also no manifest indication that frankly hypogonadal elderly cannot respond to the treatment.

5. Cognitive function. Janowsky *et al.* (492) in a small-scaled study observed in elderly men with low FT an improved working memory after 1 month of im administration of testosterone (n = 10) compared with placebo (n = 9) using the Subject Ordered Pointing Test for which the authors found in the absence of treatment a worse performance in the elderly as compared with the young but no gender effect. The same group reported that in elderly men with FT "normal for age," administration of testosterone by scrotal patch (n = 27) enhanced compared with placebo (n = 29) spatial cognition assessed by the block design subset of the Wechsler Adult Intelligence Scale, but was without effect on verbal and visual memory, cognitive flexibility, or fine motor dexterity. In community-dwelling older men not selected on the basis of their androgen status, Cherrier *et al.* (493) found that 6 wk of im testosterone treatment (n = 13) improved compared with placebo (n = 12) several aspects of cognition, although treatment effects were not evident for all performed measures; positive effects were observed for spatial ability according to block construction testing, spatial memory according to recall of a walking route, and verbal memory according to the recall of a short story. Three months of DHT administration to elderly men with borderline low serum testosterone (n = 17) was not different from placebo treatment (n = 18) for performance on a battery of cognitive tests in the study of Ly *et al.* (470). In a small study in elderly men with mild cognitive deficit and moderately low serum bioT, Kenny *et al.* (494) observed no effect on cognitive performance of 12-wk im testosterone (n = 6) compared with placebo (n = 5).

As to trials of longer duration, Sih *et al.* (458) failed to observe in older men with moderately low androgen levels an effect of 12 months of im testosterone administration (n = 17) *vs.* placebo (n = 15) for a battery of cognitive function tests. In the study by Kenny *et al.* (486), treatment of elderly men with moderately low bioT for 12 months with testosterone patches did not result in significant treatment effect *vs.* placebo for cognitive tests including the Digit Symbol, the Digit Span, and the Trailmaking A and B; there was for Trailmaking B an improved score compared with baseline in the testosterone-treated group and an association of the posttreatment scores with serum testosterone levels in the combined active treatment and placebo groups.

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.

6. Mood and quality of life

a. Mood and depression. Several trials with androgen treatment included questionnaires on mood and/or depression. These studies failed to demonstrate a treatment effect on either mood (467, 491, 492, 495) or scores for geriatric de-

pression scales (458, 494), with the single exception of the observation in the small study by Bakhshi *et al.* (480) of a larger improvement of the score for a geriatric depression scale in the active treatment group (n = 9) than in the placebo group (n = 6) in male geriatric patients admitted for revalidation.

b. Quality of life. In a small study, elderly men with moderately low serum androgens treated for 1 month with testosterone failed to accurately guess treatment assignment (492), whereas in another study 6-month treatment with DHT gel failed to improve the score of a questionnaire on general well-being (491). Several studies assessed health-related perception of quality of life using the Medical Outcome Survey (MOS) Short Form 36 (SF-36) questionnaire (467, 468, 470, 481, 486, 490, 496). The findings in the latter studies were mostly negative (467, 470, 486, 490, 496). One exception was the report of significantly less worsening of the perception of physical function in elderly men treated for 3 yr by testosterone scrotal patches compared with placebo-treated subjects in the study by Snyder *et al.* (468). Interestingly, improvement of the score for perception of physical health during active treatment was inversely correlated to pretreatment serum testosterone levels (Fig. 7), but it should also be noted that physical health perception is only one of eight dimensions assessed by the SF-36 questionnaire. The only other exception was the finding by English *et al.* (481) of improved scores on pain perception and role limitation resulting from physical problems during testosterone administration to elderly men with CAD. In men requiring long-term systemic glucocorticoid treatment, Crawford *et al.* (463) found that treatment with testosterone, but not with nandrolone, improved overall quality of life as assessed with the Qualeffo 41, a dedicated questionnaire for patients with osteoporosis.

In summary, the findings for treatment effects on mood, depression, and quality of life in elderly men are mostly negative. It remains to be established in how far the failure to demonstrate beneficial effects may have resulted from the use of instruments that are insufficiently sensitive to detect changes in study populations consisting of men with rather good general health status. Nevertheless, it can be noted that the few positive results were all obtained in men with impaired health (463, 480, 481) or in a subset of men with manifestly low serum testosterone (468).

C. 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 (428, 431).

Except for short-term anabolic treatment in situations with (risk of) frailty such as in elderly men undergoing major surgery, where use of high doses of testosterone has been reported (479), proposed use of androgens in the elderly usually aims at so-called "substitutive treatment" resulting in sex steroid levels approaching or mimicking physiological androgen and estrogen levels in younger men. Therefore, we discuss here possible side effects of chronic treatment with "near physiological" doses of testosterone or DHT only, keeping in mind however that many of the proposed treatment regimens might in fact result in moderately supraphysiological mean serum sex steroid levels or in intermittently markedly elevated levels in particular relative to what might be the physiological requirements for the elderly, which is still poorly defined.

1. 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 (497), but, because almost all prostatic carcinomas are androgen sensitive (498, 499), it is evident that the presence of a clinical carcinoma is an absolute contraindication for androgen substitution.

The crux of the problem, however, constitutes the clinically and biochemically occult subclinical carcinoma, which appears to be present in the majority of subjects over 60 yr old (500). Only a small percentage will evolve during lifetime into a clinical carcinoma, but one has to consider the possibility that androgen substitution might stimulate this evolution. Prospective epidemiological studies, however, did not reveal large differences in circulating hormone levels between men who subsequently developed prostate cancer and those who did not (501, 502), and so far the very limited data from the few studies involving treatment of at least 1-yr duration did not yield alarming findings (439, 458, 459, 461–463, 477). However, in the informative trials including specifically elderly men that we have identified (Table 4), no more than 201 elderly men actually received active testosterone treatment intended to last for at least 1 yr and, inevitably, even among these rather few men there were occasional cases of prostate cancer diagnosed during treatment (459, 461). Data on the effects of long-term treatment are not available. It has been calculated that to detect a 30% difference in prostate cancer incidence between placebo- and testosterone-treated subjects, 6000 older men with low testosterone would need to be randomized to each treatment group and would require treatment for an average of 5 yr (430). In any case, vigilance about the risk of prostate cancer is required even in men with low basal testosterone level, any increase of prostate-specific antigen (PSA) levels greater than expected in healthy men necessitating urology consultation and eventually a prostate biopsy. Most studies show a slight increase of PSA levels, which usually remain within the normal range (419, 446, 459, 461, 462, 478, 490, 503). Nevertheless, some men with initially normal clinical findings and serum PSA do show pathological increases requiring further investigation. Although the cut-off value for PSA increment velocity that should trigger additional diagnostic steps varies according to authors (430), it seems logical to be particularly attentive to changes that exceed the expected interassay variability and a cut-off value of 0.75 ng/ml per year seems reasonable (504).

As to benign prostatic hyperplasia (BPH), a highly prevalent finding in elderly men, although androgen substitution causes a small increase of prostate volume in particular in hypogonadal men, no increase in voiding symptoms or re-

sidual urine volume has been reported (419, 458, 461–463, 477, 479, 490). Although in men with BPH causing only mild symptoms, androgens can be administered safely, obstructive BPH is a contraindication for treatment (430, 505).

There is evidence that 7α-methyl-19-nortestosterone, which is not being 5α-reduced, acts more selectively and might stimulate less prostate tissue (464, 506). On the other hand, because estrogens are considered to play a role in the development of BPH, it has been suggested that use of DHT, which is not aromatized, might be advantageous as far as prostate side effects are concerned (461, 491). Nevertheless, increase of endogenous testosterone production with lowering of estrogen synthesis by administration of an aromatase inhibitor did result in increased PSA levels (490).

In conclusion, when considering testosterone administration to elderly men, digital rectal examination of the prostate and PSA determination are required, and whenever clinical abnormalities or PSA levels above 4 ng/ml are found, additional urological exploration is mandatory. After initiation of therapy, control of the prostate with digital rectal examination and PSA determination after 3, 6, and 12 months and annually thereafter is being recommended (430, 431, 505).

2. 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% (419, 454, 458, 459, 461, 462, 470, 477–479, 507). Erythrocytosis might increase the risk of stroke and requires corrective measures, *i.e.*, temporary interruption of treatment, dose adaptation, and/or phlebotomy. Testosterone treatment by im injection might be associated more frequently with eryhtrocytosis than the transdermal route of administration, most likely because traditionally applied treatment regimens with im injection of testosterone esters at biweekly to monthly intervals result in serum testosterone levels that are transiently, but markedly supraphysiological after each injection (458, 508).

Hematocrit or hemoglobin blood concentration should be determined at initiation of treatment and at follow-up visits (431), with close monitoring of men at higher risk of erythrocytosis such as those with chronic pulmonary disease.

3. 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. As has been discussed in *Sections III.C.3 and V.B.3* and has been reviewed extensively by others (322, 323, 431), when considering variations within or close to the physiological range, higher serum testosterone levels cannot be equated to a higher risk of atherosclerosis and CAD. The trials with androgen treatment aiming at near-physiological levels revealed neither worrying effects on cardiovascular risk factors such as lipid levels nor an increased incidence of cardiovascular or cerebrovascular adverse events. However, the number of elderly men treated in a controlled setting is very small, with an only short duration of observation.

In conclusion, the data from observational and interventional studies do not indicate major reasons for concern, but the safety of androgen therapy in elderly men should not be considered as established before an adequately powered prospective study with major cardiac and vascular events as endpoint has been performed. The significance of the latter hiatus in our understanding of the risks and benefits of androgen administration for its potential widespread clinical application should in no way be minimized considering that cardiovascular disease is the leading cause of morbidity and mortality in elderly men.

4. Sleep apnea. There have been rather anecdotal reports that androgen treatment can induce or exacerbate sleep apnea (509, 510), which might be especially the case in obese subjects, patients with COPD, and smokers. Liu *et al.* (467) 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 prolongation of periods of hypoxemia, although for the short duration of the study there were no manifest consequences in terms of functionality and well-being. In the study by Snyder *et al.* (461) in elderly men with low normal to moderately low serum testosterone, monitoring of sleep apnea did not reveal differences between the men treated with testosterone by scrotal patches and the placebo controls (458). Nevertheless, it seems advisable to inquire about symptoms of sleep apnea both before treatment and at follow-up visits (479).

5. Other adverse effects. Clinically significant fluid retention and hypertension are seldom observed with moderate doses of testosterone (431), 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 (431) 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 development 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 (431).

6. Comment. Finally, it should be pointed out that 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.* (427) observed a higher incidence of erythrocytosis, leg edema, and prostate events in the elderly, whereas the young had more frequently

acnea. 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 (27, 511).

D. DHEA treatment

The impressive age-associated decline of plasma DHEA and DHEAS levels as well as a broad array of reported beneficial effects of (pharmacological doses) DHEA in laboratory animals have raised the hope that DHEA supplementation in elderly men might have favorable effects on sexual, vascular, metabolic, immune, and cognitive functions. In fact, DHEA supplementation has been advertised in the media as an antiaging, rejuvenating medication without, however, much scientific justification.

Few large-scale placebo-controlled studies on the effects of DHEA supplementation in males are available. In 1994, Morales *et al.* (512), in a randomized, placebo-controlled, crossover trial with 50 mg/d DHEA administered orally for 6 months to 13 men aged 40–70 yr (mean, 53.7 ± 2.5 yr), observed a "remarkable increase in perceived physical and psychological well-being," without change in libido or lipoprotein profile; they observed an increase in plasma IGF-I and a decrease in IGF binding protein (IGFBP)-1 levels. In a more recent randomized, placebo-controlled, crossover trial with administration of 100 mg/d DHEA for 6 months, which involved only nine men (mean age, 55.6 ± 1.9 yr), the same authors observed a small decline of fat body mass (by 1 ± 0.4 kg) and an increase of knee and back muscle strength; IGF-I levels increased, but IGFBP-1 levels remained unchanged (513). In another small-scaled study that was not randomized and involved eight men 72 ± 2 yr old receiving 50 mg of DHEA daily for 6 months, a decrease in fat mass and an increase of spine and total body BMD was observed with increase of serum IGF-I without change in IGFBP-3 levels (514). However, a series of well-conducted trials failed to confirm these reports of beneficial effects.

In a randomized, double-blind, placebo-controlled crossover study over 9 months with 3 months of treatment with 50 mg micronised DHEA twice daily in 39 men aged 60–84 yr, Flynn *et al.* (515) did not observe any significant change in physical or psychological well-being, perceived satisfaction in activities of daily life, libido, or sexual function. Neither were there significant changes in body composition; there was a small increase in total cholesterol and HDL-C. Besides the expected rise in serum DHEA(S) concentrations, treatment resulted in a clear increase of estradiol and FT levels without change in serum total testosterone. The latter findings are in agreement with the observations of Arlt *et al.* (516) that administration of 50 or 100 mg/d of DHEA to 14 volunteers aged 58.8 ± 5.1 yr resulted in increased serum concentrations of FT, androstenedione, and estradiol without significant alteration of total testosterone levels; in another pharmacokinetic study, administration of 50 mg/d DHEA to 12 elderly men aged 67.8 ± 4.3 yr resulted is nonsignificant changes in serum total testosterone and estradiol with marked increase of estrone levels (517).

Arlt *et al.* (518) found that administration of 50 mg DHEA daily for 4 months to 22 elderly men aged 50 to 69 yr in a randomized, placebo-controlled, crossover trial had no effect on mood, sexuality, serum lipids, biochemical markers of bone turnover, body composition, or exercise capacity. Baulieu *et al.* (354) reported the results of the largest double-blind, placebo-controlled study, which involved 140 men 60–80 yr old, 66 of whom received 50 mg of DHEA daily for 1 yr. They did not observe any effect on BMD or biochemical markers of bone turnover, nor did they observe any effect on libido, sexual activity, or vascular properties. They observed only an increase in sebum production and skin surface hydration. Other recent studies gave similar negative results. Kahn and Halloran (519), administering in a randomized, placebo-controlled, double-blind, crossover study design 90 mg of DHEA daily for 6 months to 43 men (56–80 yr old), did not find any evidence for an effect of DHEA on bone turnover.

As to the effects of DHEA on cognitive functions, Wolf *et al.* (520) in a short-term randomized, placebo-controlled, crossover trial of 2-wk duration involving 25 men (mean age, 69.4 ± 1.2 yr) receiving 50 mg/d of DHEA, did not see any beneficial effects on measured psychological or cognitive parameters, whereas van Niekerk *et al.* (521), after 13 wk of treatment with 50 mg micronised DHEA daily in 41 men (60–80 yr old) according to a double-blind, placebo-controlled, crossover study design, did not observe significant differences for any of the outcomes (object location, mood, well-being) between the DHEA and the placebo phase, in agreement with data of Kudielka *et al.* (522). Because DHEA is a neuroactive neurosteroid (523), it has been suggested that DHEA might be of clinical usefulness in age-related dementia, but treatment of Alzheimer's disease with 100 mg/d DHEA for 6 months in 28 patients (14 men) aged 75.5 ± 8.4 yr yielded disappointing results and was not associated with significant improvements in cognitive performance compared with the placebo-treated subjects (n = 30) in a randomized, double-blind study (523).

Liu and Dillon (14) described recently an endothelial plasma membrane receptor for DHEA, which could suggest that DHEA supplementation can influence endothelial function. Kawano *et al.* (524) in a study that involved 24 men aged 54 ± 1 yr with hypercholesterolemia observed that 25 mg/d of DHEA for 12 wk induced an improvement of flow-mediated vasodilatation dependent on endothelium-derived nitric oxide; concomitantly, a decrease of the plasma level of plasminogen-activator-inhibitor, a factor regulating fibrinolysis, was observed with suggestive evidence of improved insulin sensitivity. The latter observation is in contradiction with the data of Morales *et al.* (512) and Flynn *et al.* (515) who did not observe any effect of DHEA on insulin sensitivity.

On the basis of the effects observed in laboratory animals, favorable effects of DHEA on the immune response have been postulated (525, 526), but whereas Araneo *et al.* (525) observed in 67 elderly men (<65 yr old) a trend for improvement of immunization to influenza vaccine by treatment with DHEA (2 × 50 mg/d for 4 d), Danenberg *et al.* (526) after a 4-d short-term treatment of elderly men (age, >60 yr; n = 71) with 50 mg DHEA daily could not demonstrate any improvement of the age-associated decline of response to immunization against influenza.

In summary, the data on DHEA supplementation of

healthy elderly males do not show convincing evidence for any beneficial effect on any physical or psychological parameter. In the biological findings, besides increases in serum estrogens and FT, only IGF-I levels showed a consistent increase, the clinical significance of the latter finding being questionable. Nevertheless, DHEA supplementation might have some beneficial effect in males with Addison's disease, who lack DHEA secretion. Indeed, DHEA substitution in these patients was reported to induce improvement of mood, fatigue, and general well-being, but no effects were seen on cognitive or sexual functions, body composition, BMD, or lipids and separate data for male patients have not been reported in detail (527). As to safety of DHEA treatment, significant side effects were not observed with up to 100 mg DHEA/d for 1 yr.

VI. Summary and Conclusions

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 interindividual 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 in our ability 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 fulfil 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, practical recommendations having been reviewed elsewhere (428, 430, 431, 438).

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