

COMMENTARY

Androgen Replacement Therapy in the Aging Male—A Critical Evaluation

A. VERMEULEN

Department of Internal Medicine, Section of Endocrinology, University Hospital, 9000 Gent, Belgium

Recent years have seen an increasing interest in the study of the aging male, with a particular interest in the problem of whether so-called rejuvenating hormones and, more specifically, androgens can improve quality of life, counteract progressive skeletal muscle loss and strength, prevent falls and fractures, prolong independent living, and reduce the dependence on medical care.

Almost a decade has elapsed since the first studies on androgen supplementation in elderly men were published (1, 2) and, in the view of the persisting controversies concerning this problem as well as the increasing public interest for rejuvenating hormones, it may be indicated to evaluate critically the clinical relevance of the relative androgen deficiency in elderly males, the diagnostic criteria of androgen deficiency, as well as the risks and benefits of androgen supplementation in elderly men.

Male hormone replacement therapy implies, of course, that elderly men have a significant deficit in male hormone. Therefore, the first question to be answered is whether the common occurrence of the age-associated decline of testosterone levels is inherent to the aging process and occurs also in healthy men or whether the observed decline is the consequence of intercurrent disease, obesity, stress, relative physical inactivity, medications, etc.

After years of controversy, due to differences in the characteristics of the population studied and variation in the timing of blood sampling (morning or afternoon) or the frequently small number of elderly subjects studied, authors now agree that in healthy men also there is a clear, slow but continuous, age-dependent decline of testosterone (T) levels, which is more pronounced for free T (FT) than for total T, a consequence of the age-associated increase of the levels of sex hormone binding globulin (SHBG); at 75 yr of age mean total T level in the morning is about two thirds of the mean level at 20–30 yr of age, whereas the mean FT and bioactive T (FT plus albumin bound T) level are only 40% of the mean levels in younger males. Moreover, the circadian rhythm of plasma T levels, with higher levels in the morning than in the evening, is generally lost in elderly men (3). However, wide

interindividual variations exist due to genetic factors, body mass index, diet, social habits (alcohol, tobacco), and stress, and about 20% of males over 70 yr old have T levels in the upper third of males 20–40 yr of age (4). This is in clear distinction to the situation in postmenopausal women who all have clearly decreased estradiol levels. It is important to mention that this decrease, observed in cross-sectional studies, has now been confirmed by longitudinal studies (5–9). However, the androgen deficiency in elderly men is generally moderate; therefore, some authors have suggested the term partial androgen deficiency in the aging male (PADAM). Others, in analogy with the term menopause in women, use the term andropause, although distinct from women in menopause, elderly men retain their reproductive capacity.

Although the decrease in (F)T levels occurs in healthy elderly men, it is evident that sequelae of intercurrent disease (10), medication, environmental, psychosocial, and socioeconomic factors accelerate this age-associated decrease. Recently, the important role of abdominal obesity in the age-associated decrease of T levels has been stressed (10–12).

Clinical significance of the age-associated decline in androgen levels in elderly men

Androgens have many physiologic actions, but does the age-associated decrease in (F)T levels have clinical significance, and does it indicate hypogonadism? Evidence for the clinical significance could be provided by the eventual similarity between signs and symptoms of aging and androgen deficiency, respectively, in young men, the existence of a significant correlation between symptoms and (F)T levels, and the eventual beneficial effect of androgen supplementation in elderly men with low T levels.

Similarity of signs and symptoms of aging and androgen deficiency, respectively, in young men. The age-associated decrease in muscle mass and strength, energy and work capacity, body hair, and hematopoiesis; the decrease in sexual drive and activity, bone mass, and cognitive function; the decline of memory and of the sense of general well being; the difficulties in concentration; and the increase in abdominal fat mass are reminiscent of the symptomatology of androgen deficiency. However, these symptoms are multifactorial in origin; aging is accompanied by a decrease of almost all physiological functions and, as far as the endocrine system

Received December 19, 2000. Revision received March 20, 2001. Accepted March 20, 2001.

Address correspondence and requests for reprints to: A. Vermeulen, M.D., Department of Internal Medicine, Section of Endocrinology, University Hospital, 185 De Pintelaan, 9000 Gent, Belgium. E-mail: Alex_Vermeulen@hotmail.com.

is concerned, by a decrease not only of gonadal and adrenal androgen secretion but also of GH secretion. Moreover, the age-associated decrease in physical activity is partly responsible for the decrease in muscle mass and bone mineral density (BMD) (13). Hence, it is not surprising that the correlation between aging symptoms and T levels is often rather poor.

Correlation between aging symptoms and (F)T levels. Whereas the age-associated decrease of BMD with an exponential increase in bone fracture rate with age (14, 15) is well established, the role of the partial androgen deficiency in aging males in this decrease remains to be established (16). Indeed, available data are equivocal, some studies showing a significant, albeit weak, association between FT levels and BMD at some but not all bone sites (13, 17, 18), whereas others did not find any correlation (19–21). Recently, several large-scale studies, involving several hundreds of elderly men (22–24), found bio-T to be significantly associated with bone density at radius, spine and hip; however, the correlation with bioestradiol, the levels of which decline in elderly males, was even stronger, suggesting that part of the androgen effects on bone are at least partially indirect, mediated via their aromatization (25). Nevertheless bio-T also was correlated with all regions of proximal femur BMD and total body BMD after adjustment for age (24). Barrett-Connor *et al.* (26) observed a significant negative graded association between levels of total and bioavailable estradiol but not bio-T and fracture prevalence in males (median age 67 yr, range 56–87 yr) independently of age, body mass index, or exercise.

On the basis of these recent large-scale studies it seems reasonable to accept a role of the decreased T levels in the age-associated osteopenia.

Aging is also accompanied by an increase in abdominal fat mass and a decrease of muscle mass. We (27) as well as Seidell *et al.* (28) and Tchernof *et al.* (29) observed abdominal fat mass to be inversely correlated with FT, independently of age. Visceral fat accumulation is highly significantly associated with increased risk of cardiovascular disease, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus (syndrome X) (30, 31). Whether the abdominal obesity is the consequence of the low T levels or vice versa is not clear. Indeed, obesity induces a decrease of T levels via a decrease in SHBG levels, and morbid obesity (BMI >35) also induces a decrease of FT (11).

The age-associated decline in muscle mass (12 kg between 20 and 70 yr of age), which is most pronounced for the fast twitch type II fibers (32), is a major contributor to the age-associated decline in muscle strength and early onset of fatigue (33) and a strong predictor of falls, fractures, and loss of independent living. In fact, maximal muscle strength correlates with muscle mass independently of age (34)

Whereas van den Beld *et al.* (24) observed that in men 73–97 yr of age, serum T levels were, independently of age, positively related to isometric grip strength and leg extension strength, and Abassi *et al.* (35) observed a correlation between T levels and severity of loss of muscle function in institutionalized men who have lower T concentrations than healthy elderly men, Baumgartner *et al.* (36) observed in elderly men (65–97 yr old) a significant correlation between FT and muscle mass, but not grip strength. Verhaar *et al.* (37),

similarly, did not find any association between T levels and muscle strength.

It should be stressed that although a correlation exists between the lower T concentration and reduced muscle function in older men, T is not the only factor responsible for the age-associated muscle loss.

The prevalence of atherosclerosis in men increases spectacularly with aging. In the view of the higher prevalence in men than in women, the decrease of high density lipoprotein cholesterol (HDL-C) levels at puberty in boys (38), the atherogenic lipid profile in hirsute women, and the sporadic reports of premature cardiovascular disease in athletes abusing anabolic/androgenic steroids, this difference is generally considered to be related to the higher androgen levels in men. Nevertheless, the vast majority of cross-sectional studies show a positive correlation between FT levels and HDL-C (39–41) and a negative correlation with fibrinogen, plasminogen activator inhibitor-1 (42), and insulin levels as well as with coronary heart disease (43, 44), but not with cardiovascular mortality (45–47). However, the correlation between T levels and HDL-C and insulin sensitivity is only observed within the physiological male concentration range of T (48, 49). Androgen blockade by GnRH leads to an increase of HDL-C and, to a lesser extent, of total cholesterol, the effect of which is neutralized when T enanthate was injected in parallel, to maintain physiological T concentrations (48), whereas supraphysiological T levels induce an increase in low density lipoprotein cholesterol (LDL-C) and a decrease of HDL-C (40). Moreover, it should be realized that, beside the effects on lipids, T has direct effects on several vasoactive factors such as endothelin (50), prostacyclin, and thromboxane A₂ (51).

The inverse correlation between T levels and the severity of coronary artery disease as reported by Phillips *et al.* (43), may be related to the fact that low androgen levels are accompanied by an accumulation of abdominal visceral fat (28, 29), which is known to be associated with increased cardiovascular risk factors (52), and Tchernof *et al.* (29) observed that upon multivariate analysis, adjusting for visceral obesity, the correlation between androgen levels and lipid parameters lost its significance.

As to the role of the age-associated decline in T levels in the highly negative correlation between sexual desire, arousal, activity, and age, Schiavi (53) reported that men desiring intercourse with a greater frequency than once a week, had higher T levels than men with lower frequency. Moreover they observed (54) that men with the primary diagnosis of hypoactive sexual desire had significantly lower T levels than controls. Similarly, Pfeilschifter *et al.* (55) reported that men with greater sexual activity had higher bio-T levels than men with a lower frequency and they conclude that androgen deficiency may contribute to the age-related decline in male sexuality. Nilsson *et al.* (56) finally, in an epidemiological study of 500 51-yr-old men, observed that low levels of bio T were associated with low sexual activity.

However, other authors (57, 58) did not observe any correlation between plasma T levels within the normal range and sexual activity. Moreover, it is known that healthy males have much higher T levels than required to maintain sexual function, although Schiavi (53) as well as Bancroft (59) suggested that circulating androgen levels in elderly men might

be insufficient to sustain nocturnal penile tumescence and adequate sexual function.

As to erectile dysfunction, which increases dramatically with age, whereas androgens, acting both centrally and peripherally (60) are essential for normal penile erection and T-stimulating nitric oxide synthesis in the corpora cavernosa (60, 61), androgen deficiency is rarely the major cause of impotence in elderly males, although it may play a subsidiary role. There is good evidence that, whereas nocturnal penile tumescence is androgen dependent, erection in response to visual erotic stimuli is androgen independent (62). Davidson *et al.* (63) suggested that the effects of T may be mediated via changes in genital sensitivity.

Finally there is good evidence for a strong correlation between T levels and cognitive performance such as spatial abilities or mathematical reasoning (64, 65), findings which were confirmed in Western and non-Western groups of healthy males (64). Studies addressing correlations between T levels and cognitive functions specifically in elderly men are not available.

As to the role of T in the depressed mood frequently observed in elderly men, whereas data in the literature are rather divergent [for review see Christiansen (66)], a recent large study by Barrett-Connor *et al.* (67) involving 856 men age 50–89 yr showed a significant inverse correlation between bioavailable T and a depression score, independent of age and weight.

In summary, many aging symptoms in men are suggestive of androgen deficiency and, in fact, there frequently exists a weak correlation of these signs with plasma T levels; many, but not all, studies show the persistence of these correlations after correction for age.

Nevertheless, it should be kept in mind that most of the aging symptoms are multifactorial in origin and that the age-associated decrease in GH levels might play an important role in the symptomatology (68), because symptoms of GH deficiency in young men and the symptoms of aging again show a striking similarity; decrease in muscle mass, increase in abdominal fat, thinning of the skin, asthenia, and adynamia.

Aging and adrenal androgens

Aside from a decrease in the secretion and plasma levels of T, aging is accompanied by a decrease of the plasma levels of the major adrenal androgen, dehydroepiandrosterone sulfate (DHEAS). The age-associated decrease is the most important decrease of all hormones; at 75 yr of age, mean DHEAS levels are only 20% of levels in young adults and, whereas rather important interindividual variations exist, all men and women show an important age-dependent decrease (69–71).

Does this decrease have clinical significance? Although it has been reported that in animals that do not secrete DHEAS, administration of DHEAS generally in pharmacological doses, has antiatherogenic, immunostimulatory, and anticarcinogenic effects, the effects of DHEAS in man remain questionable. Functional parameters of daily living in the oldest males were reported to be lowest in men with the lowest DHEAS levels (72), whereas data of Abassi *et al.* (73)

show that men with higher DHEAS levels appear to be more fit and leaner than men with lower DHEAS levels. This, of course, does not indicate a causal role of DHEAS in physical fitness or general well-being. Moreover, it has been reported that men with low DHEAS levels would be at higher risk of cardiovascular mortality within the next 2 yr (74, 75), but this has not been confirmed (76, 77). Finally, the increase in physical well-being after DHEAS administration reported by some authors (78) was not confirmed by others (79), but there is some evidence that DHEAS administration to men with Addison's disease improves general well-being (80, 81).

Hormone replacement therapy

Diagnosis of androgen deficiency in elderly males. As the clinical symptoms of hormone deficiency in elderly males are rather vague and aspecific and as a substantial number of elderly men have (F)T levels within the normal range for young adults, we can state that hormone replacement therapy (HRT) is only warranted in the presence both of clinical symptoms suggestive of hormone deficiency and of decreased hormone levels. Moreover, eventually present primary causes of the decreased androgen levels should be adequately treated before starting HRT.

How do we define hypogonadism in elderly males? Clinical signs of relative androgen deficiency in elderly men most easy to objectify are a decrease of muscle mass and strength, a decrease of bone mass and osteoporosis, and an increase in central body fat. Other signs such as a decrease in libido and sexual desire, forgetfulness, loss of memory, difficulty in concentration, insomnia, as well as a decreased sense of well-being are rather subjective impressions that are more difficult to measure and differentiate from hormone-independent aging.

As to subnormal (F)T levels, it should be realized that it is still unknown whether the requirements of elderly males are identical with the requirements of younger men. There is some evidence for increased sensitivity to androgens in elderly males, for example, at the level of the feedback system (82–85), whereas several (86–91), but not all (92, 93), studies show a decrease of the androgen receptor (AR) concentration in tissues of elderly animals and men, suggesting a saturation of the receptor sites at a lower T concentration and a decrease of the maximal genomic effect of T. Also, changes in the CAG repeat length of the AR gene may be involved in the age-related decline of plasma T levels. The latter appear to decline more rapidly in subjects with a lower number of CAG repeats (7). This is possibly the consequence of a higher androgen sensitivity; a large number of CAG repeats as in the Kennedy syndrome are accompanied by androgen resistance and increased T levels.

Moreover, even in the young men, it is not clear whether T concentrations in the normal range are required for full androgenic effects in the different androgen-responsive organs. It has been reported repeatedly that T levels at half the concentration found in young males, are appropriate for sustaining normal libido and sexual activity (94).

In fact, there is no clinically useful biological parameter reflecting androgen activity. It has been suggested that SHBG capacity might be such a parameter (95) but, whereas the

decrease of SHBG after T treatment indicates androgen activity, a single basal SHBG level is difficult to interpret; the level is determined by several hormonal and nonhormonal factors, such as GH, insulin, thyroid hormones, obesity, and medications.

It should be realized, finally, that normal hormone levels do not imply *per se* normal physiological effects; indeed, the interaction of the ligand with the hormone receptor as well as the presence of coactivators and coinhibitors will determine the biological effects.

Because there is no generally accepted cut off value of plasma T for defining androgen deficiency, and in the absence of convincing evidence for an altered androgen requirement in elderly men, we consider the normal range of (F)T levels in young males also valid for elderly men. In our healthy male nonobese population 20–40 yr of age ($n = 150$), the mean of log-transformed early morning T levels was 21.8 nmol/L (627 ng/dL), the mean $- 2$ SD was 12.5 nmol/L (365 ng/dL), and the mean $- 2.5$ SD was 11 nmol/L (319 ng/dL). For FT, measured by equilibrium dialysis or calculated from T and SHBG levels (96), the mean was 0.5 nmol/L (14 ng/dL), the mean $- 2$ SD was 0.26 nMol/L (7.4 ng/dL), and the mean $- 2.5$ SD was 0.225 nmol/L (6.5 ng/dL). If we take as the lower normal limit and threshold of partial androgen deficiency, a conservative value of 11 nmol/L for T and 0.225 nmol/L for FT, which represent the lower 1% value of healthy young males, then it appears that more than 30% of men over 75 yr old have subnormal (F)T levels. Most authors use rather similar values (1, 2, 9, 13, 97, 98). It should be mentioned that direct FT assays using a T analog, do not yield a reliable estimate of FT (96). The age-associated decline in (F)T levels has both a testicular (decreased Leydig cell number) and central origin, the latter being characterized by a decrease in the amplitude of LH pulses in elderly men. Hence, many elderly men have normal LH levels and we do not consider an increase in LH levels to be required for the diagnosis of hypogonadism in elderly men (84). As already mentioned, in the absence of a reliable, clinically useful biological parameter of androgen action, these criteria of hypogonadism of the aging men are somewhat arbitrary.

The treatment aims at restoring hormone levels in the normal range of young adults and, more importantly, at alleviating the symptoms suggestive of the hormone deficiency. However, the ultimate goals are to maintain or regain the highest quality of life, to reduce disability, to compress major illnesses into a narrow age range, and to add life to years.

What are the effects of androgen supplementation in elderly man with subnormal (F)T levels? Before discussing the beneficial effects of androgen supplementation in elderly males, it should be stressed that the number of well controlled studies is still small; the number of patients having been involved in such studies is limited to a few hundred. Hence the experience is limited and the clinical results should be interpreted critically.

There is no doubt that in young androgen-deficient men T supplementation increases fat free mass and muscle strength and decreases body fat, with improvement of insulin sensitivity (98, 99–104). Androgens induce their spe-

cific response via the AR, which regulates the androgen-responsive target genes. Following androgen treatment, Sheffield-Moore *et al.* (105) observed an increase in AR messenger RNA in healthy young men, and in older men long-term androgen administration increased AR transcription at 1 month with a return to base line levels after 6 months (105, 106). Androgen administration to healthy older men increased insulin-like growth factor 1 messenger RNA; decreased the concentration of the inhibitory insulin-like growth factor binding protein 4 (107); and, increasing protein synthesis (99, 105–107), induced myotrophic effects in skeletal muscle (104, 105).

After androgen supplementation to elderly men, generally at a biweekly dose of 200 mg T enanthate, several authors (1, 2, 106, 108) reported a significant, albeit often relatively modest, increase in muscle mass (± 2 kg) (1) and/or arm circumference and generally of grip strength, whereas fat mass generally is decreased modestly (106, 109). Also Urban *et al.* (106) reported that T administration to elderly men increases skeletal muscle strength. A recent study of Snyder *et al.* (97), on the other hand, reported an increase in lean body mass (LBM) but without increase in strength of knee extension or flexion, whereas Clague *et al.* (110) after a 12-week administration of T, found neither an increase of LBM nor muscle strength.

Bhasin *et al.* (111) stresses that although muscle strength is an important aspect of muscle function, it is not the most important. Muscle power, defined as the rate of power development is strongly correlated to performance of functional activities such as rising from a chair, stair climbing, *etc.*; such an increase, more specifically of the lower limb muscles, would be important, improving mobility and stability and preventing falls and, hence, fractures (110).

As to osteoporosis, all studies show that in hypogonadal men androgen supplementation increases bone mass (100, 102, 103, 112), although normal adult bone mass is not reached (113). Also in eugonadal men with osteoporosis, T esters (250 mg/2 weeks) increased BMD (114). Again, the effects in elderly men are less convincing. Morley *et al.* (2) observed an increase in osteocalcin levels, an index of osteoblast activity, whereas Tenover (1) reported a decrease of hydroxyproline excretion, an index of bone resorption, and more recently (Tenover J. S., personal communication) in a 3-yr study involving 70 elderly men, an increase in BMD at all measured sites. However, neither Orwoll and Klein (14) nor Sih *et al.* (108) could observe any effect of T supplementation on biochemical parameters of bone turnover. Snyder *et al.* (115), in a study involving 108 elderly subjects, observed that HRT increased BMD of the lumbar spine, but not of the hip, in patients with clearly subnormal T levels, but not in the whole elderly population studied, which included, all subjects with a T level below 16.5 nmol/L (475 ng/dL), a value which certainly is not in the hypogonadal range. On the other hand, it is evident that morbidity of osteoporosis relates essentially to hip fractures! It may be of interest to mention that in orchidectomized aged rats, the threshold concentration of T, necessary for prevention of loss of both bone and LBM is clearly lower than for prostate and seminal vesicles (116). Whether this applies also to the aged man requires further research, but would explain that the effects of T on

BMD of elderly men, are limited to men with clearly decreased (F)T levels.

Finally, HRT only makes sense when other causes of osteoporosis, such as insufficient calcium or vitamin D intake have been excluded (117).

As to the effects of T replacement on sexual activity, the effects in young hypogonadal men are spectacular (98, 101, 103), but supraphysiological doses of T administered to young healthy men for contraceptive purposes did apparently not affect frequency of intercourse, kissing, or fondling (118). Anderson *et al.* (119), injected 200 mg T enanthate weekly for 8 weeks to normal men and observed a significant increase in sexual interest, awareness, and arousal, which was, however, not reflected in modification of overt sexual behavior, which they suggest may be more determined by social factors. Morley *et al.* (2) as well as Hajjar *et al.* (120) observed that also in elderly men T replacement improves libido substantially. Wang *et al.* (98, 121) also reported improvement of sexual function; however, their data suggests that there is a threshold level of T above which there is no further enhancement of response. Interestingly, Carani *et al.* (122), in a patient with aromatase deficiency, reported evidence that estrogen might have a role in male sexual activity, but not in sex orientation.

Most authors (98, 106, 123) observed that androgen substitution in hypogonadal males improved mood, energy, sense of well being, and friendliness, whereas T levels were negatively correlated with nervousness and irritability. These significant correlations with T levels were only observed when T levels were below the normal range, which suggests that once a minimally adequate T/dihydrotestosterone (DHT) level was achieved, further increase did not further contribute to improvement of mood (98, 123).

Similarly in elderly males, androgen replacement therapy has been reported to increase the sense of well being (2, 124, 125).

Androgen supplementation in elderly hypogonadal men improves also spatial cognition (1, 126) and verbal fluency (127, 128), but no effect was seen on memory (108).

As to the influence on plasma lipids, atherosclerosis, and cardiovascular disease, it is well known that administration of T to surgically or chemically castrated males, or female to male transsexuals (129), as well as supraphysiological T levels in men (40, 129–131) induce a decrease of HDL-C and an increase of triglyceride levels. But administration of 250 mg T im once per week for 6 months to young healthy men resulted in a decrease of total and LDL-C, as well as in a slight, nonsignificant decrease of HDL-C and in a decrease of lipoprotein(a) levels (132).

Most (1, 2, 125, 133), but not all (134), studies on androgen replacement in elderly men report a fall in total and LDL-C, with no significant effect on HDL-C and an improvement of insulin sensitivity (127, 135–137). Moreover, a tendency to a fall of arterial blood pressure has been reported (135). The mechanism of this fall in lipids might be related to the decrease in the visceral abdominal fat mass (124) under the influence of androgens, which inhibit lipoproteinlipase activity and increase lipolysis (138, 139) with improvement of insulin sensitivity and mobilization of triglycerides from abdominal fat tissue (140).

As to the influence of androgen supplementation on cardiovascular disease, Alexandersen *et al.* (141) reviewing the outcome of 30 cross-sectional studies in men, reported that most studies suggest either a favorable or neutral effect of normal T levels on cardiovascular disease in men, and they conclude that low androgen levels increase the risk of cardiovascular disease in men.

It should be remembered that the beneficial effects of physiological androgen levels on the lipid profile are limited to aromatizable androgens and that the effects of androgens on the vascular system are not limited to their indirect effects on the plasma lipids, but that T decreases lipoprotein(a) (8) and has complex effects on platelet aggregation (51), blood coagulation, and fibrinolysis, respectively (142, 143). Moreover, it has been shown that administration of T in physiological concentration increases coronary blood flow in patients with coronary heart disease (144, 145), whereas beneficial effects on endothelial function (146) and myocardial ischemia have also been demonstrated (147, 148).

Unfortunately, notwithstanding its favorable effects of T supplementation on the lipidogram, so far no influence on cardiovascular mortality has been reported (45, 46).

In summary, androgen supplementation in aging males with subnormal T levels seems to have beneficial effects on muscle mass and strength, BMD, plasma lipids and insulin sensitivity, mood, libido, and sense of wellbeing, but generally only in men with subnormal (F)T levels; no effects are generally seen above a certain threshold level of T. Moreover, beneficial effects on clinically relevant parameters such as bone fracture rates, falls, infarction rates, or cardiovascular mortality, so far, have not been reported, and the clinical significance of the observed effects remains questionable.

Surveying the data available, on one hand, one is struck by the fact that the beneficial effects of T supplementation are much more pronounced in young hypogonadal males than in elderly men, and, on the other hand, by the fact that although almost a decade has elapsed since the first clinical studies on androgen supplementation in elderly men were published, the number of elderly subjects having participated in controlled studies of androgen supplementation are very limited. We are awaiting eagerly the results of large long-term controlled studies on androgen supplementation in elderly men.

As to the first problem, this might indicate either that the elderly men receiving androgen supplementation had higher T levels at the start than the young hypogonadal men and were not really hypogonadal, which was probably the case in some studies, or that, due to a reduction of their tissue receptors, their possible response to androgens is limited. However, this is less likely as moderately supraphysiological doses appear to induce sometimes polycythemia as well as an atherogenic lipid profile. It is not unlikely that the response to androgen supplementation of the oldest men, who generally have the lowest endogenous androgen levels, would be comparable to the response of young hypogonadal men. Whether higher doses of T via nongenomic effects might be more effective is still an open question. Bhasin *et al.* (149) as well as Young *et al.* (150) observed that supraphysiological doses of T (600 mg/week im) administered for 6

weeks to normal men increased free fat mass, muscle size, and strength.

As to the limited number of studies available, this is probably related to the fear of serious side effects, more specifically, stimulation of the development of an undiagnosed prostatic carcinoma and its possible legal consequences.

Side effects of androgen supplementation. By far the most important possible side effect of androgen supplementation in elderly males is the exacerbation of prostatic disease.

T supplementation in elderly men induces only a minimal increase of the volume of the prostate with, eventually, a modest increase in levels of prostate specific antigen (PSA) (1, 2, 151). Hypogonadal men, treated for many years with T, developed a prostatic volume comparable to that of normal men of similar age (152). Hence, it appears that nonobstructive benign prostatic hyperplasia is not a contraindication for androgen substitution. However, obstructive benign prostatic hyperplasia constitutes a clear contraindication.

Because almost all clinical prostatic carcinomas are androgen sensitive, the presence of this prostatic carcinoma is an absolute contraindication for androgen supplementation. Recently, Hoffman *et al.* (153) reported the surprising finding that the levels of FT were inversely correlated with the incidence of prostatic carcinoma, and that low FT levels predicted a more aggressive neoplasm, whereas Kleinman and McKinlay (154), in the Massachusetts Male Aging Study, calculated that the hormone variables (T, FT, DHT, E₂, androstenedione) would only account for 11% of our current knowledge about prostate cancer risk *vs.* 30% for nutrition and 40% for immutable factors (age, height, and family history). In this connection it is interesting to mention that Hardy *et al.* (155) observed an inverse correlation between the length of the AR CAG repeats and the risk of early onset of prostatic cancer.

Whereas in most studies T levels in prostatic CA patients and in normal controls were similar (156), Gann *et al.* (157) in a prospective study involving 222 subjects who, within 10 yr of blood sampling, developed a prostatic carcinoma, matched with 390 controls of similar age observed when hormones and SHBG levels were simultaneously adjusted, an increased cancer risk for patients with high T levels.

A difficult problem constitutes the subclinical prostatic carcinoma, which is very frequent in elderly men (>50% of men over 70 yr old) and which is undetectable by clinical examination or laboratory techniques (PSA; transrectal ultrasonography) but only detectable by prostatic biopsy. Only a small percentage of these subclinical carcinomas will develop to a clinical carcinoma, but it is unknown whether T supplementation might stimulate its growth. There is no evidence that initiation of prostatic carcinoma is influenced by androgens. Whereas there is no geographical variation in the incidence of subclinical carcinoma (158), which is as frequent in the Far East as in Western countries, clinical carcinoma is very rare in the Far East, although (F)T levels are similar or only marginally lower in elderly Japanese men (159, 160). This suggests that physiological T levels would not stimulate a subclinical carcinoma. Nevertheless, the androgen sensitivity of all clinical carcinomas pleads for prudence

as the promotion of subclinical lesions to clinical carcinomas cannot be excluded (161).

The stimulatory effect of T on erythropoiesis is well documented. Whereas a moderate increase in hematocrit in elderly males is possibly beneficial, some studies reported an increase of the hematocrit over 51% (polycythemia) occurring in up to 25% of elderly patients (108, 120), requiring temporary withholding of the treatment and even phlebotomy. Available data suggest that the frequency of this side effect is related to supraphysiological levels (162). As transdermal patches yield T levels within the normal range, this may explain the reported lower frequency of polycythemia with this form of treatment, but more experience is required before to express a definitive opinion.

Whereas sleep apnea has been reported by Matsumoto *et al.* (163), none of the reports on T supplementation in elderly males mentioned the development of sleep apnea, which itself is often associated with lower T levels (164). Nevertheless, it is safe to consider obstructive pulmonary disease in overweight persons or heavy smokers as a relative contraindication.

As already discussed, T supplementation in physiological doses does not seem to induce an atherogenic lipid profile, but, as mentioned, T has also nonlipid mediated effects on the cardiovascular system.

Water and sodium retention generally do not cause a problem, except in patients with heart decompensation, hypertension, or renal insufficiency.

Hepatotoxicity is rare, even after the long-term use of relatively high oral doses of T-undecanoate in oleic acid (TU) (165), but is relatively frequent when synthetic 17 alkylated anabolic-androgenic steroids are used.

Gynecomastia is a benign complication of androgen supplementation, perhaps more frequent in elderly obese men than in young hypogonadal men. It is the consequence of the aromatization of T into estradiol in peripheral fat and muscle tissue.

Finally, T in supraphysiological doses suppresses spermatogenesis, but this should not be of major concern to elderly men.

Contraindications of androgen supplementation. The presence of a clinical prostatic carcinoma is an absolute contraindication for HRT and should be carefully excluded by PSA, rectal examination and, eventually, biopsy before starting any therapy.

Benign nonobstructive prostatic hyperplasia is not a contraindication, but obstructive BPH is. Polycythemia also constitutes a contraindication and the hematocrit should be controlled regularly during HRT. A rare, absolute contraindication is mammary carcinoma in the male as well as a prolactinoma, as their growth may be stimulated by HRT. Dyslipidemia is a relative contraindication requiring careful monitoring of the lipidmia during treatment.

As mentioned, COPD in overweight or heavy smoking patients often subject to sleep apnea constitutes a relative contraindication.

Modalities of androgen supplementation. The major goal of T therapy is to replace T levels as close as possible to physiologic concentrations (166).

Because orally administered T is almost completely inactivated by its first pass through the liver, the only orally active form is TU that, due its lipophilic side chain, is partly taken up by the lymph and partly escapes hepatic inactivation. The maximal plasma concentration of T is generally observed within 2–3 h, but after 6–8 h levels have returned to pretreatment levels. Hence, TU should be administered 2–3 times daily, preferably with a meal, in a dosage of $2\text{--}3 \times 40$ mg, which generally provides adequate androgen replacement, yielding T levels within the (low) normal range, whereas DHT levels are moderately increased (2–4 nmol/L) (167). However, the absorption is rather variable and the dose required should be determined on the basis of plasma levels and clinical effects. Other orally active synthetic androgen/anabolic steroids are either only weakly active (Mesterolone, Fluoxymesterone) or hepatotoxic due to the presence of an alkyl group in position 17.

The most frequently used pharmaceutical form is the intramuscular administration of the hydrophobic long chain T-esters in oily depot, enanthate and the cypionate at a dose of 200–250 mg/2 weeks. However, this yields transient supraphysiological levels the first 2–3 days after injection, followed by a steady decline to subphysiological levels just before the next injection (168). These fluctuations in T levels are recognized by some of the patients as unpleasant and accompanied by changes in energy, libido, and mood, whereas the transient supraphysiological levels might increase the frequency of side effects (162).

Preliminary studies with im injection of 1000 mg TU indicate that this treatment might yield physiological T levels during 6–8 weeks (169).

Longer acting T esters (4–6 months), such as the buciclate, are not suited for substitution in elderly males as, in case of serious side effects, a rapid withdrawal of T should be possible.

Subcutaneous T pellets (6×100 mg every 4–6 months) provide stable physiological T levels; they are not widely used and not indicated in elderly men. In about 5% of the cases the pellets are extruded, and in a similar percentage a local infection may occur (170–172).

Transdermal scrotal or permeation-enhanced nonscrotal patches, delivering 4–6 mg T per day, provide, after nightly application, physiological T levels both in young and elderly hypogonadal men (116, 162). Peak levels are obtained 2–4 h after application, decreasing afterward to two thirds of peak levels after 22–24 h, mimicking the normal circadian variation of T levels in young adults. The scrotal patches yield supranormal DHT levels (4–5 nmol/L), whereas the nonscrotal patches often cause local irritation. With a second generation torso patch (Testoderm torso patch) this, irritation would be seen less frequently. Besides providing physiological levels in young and elderly hypogonadal men (116), the patches have the advantage that the therapy can be immediately stopped when necessary (162, 173–175) Whether the increased DHT levels have deleterious effects is unknown.

A DHT gel is available (25–50 mg DHT/g) (176) at a dose of 125–250 mg/day, which yields plasma DHT levels comparable to physiological T levels; more recently it has been shown that in healthy elderly males, a lower dose of 32–64 mg/day yields comparable levels (177). DHT cannot be ar-

omatized and, whereas it will not induce gynecomastia, it is probably inactive at the bone level. Wang *et al.* (177, 178) consider that the decrease in E_2 levels by DHT gel treatment may be favorable at the level of the prostate, where estrogens stimulate the proliferation of the stroma.

Recently a 1% hydro-alcoholic T gel has become available in some countries (98, 179, 180). When administered to young or elderly hypogonadal men, 12–68 yr of age, about 9–14% of the T applied was bioavailable and with a daily application of 100 mg/day contained in 10 g gel, the plasma T levels are in the upper normal quartile; DHT levels are only slightly increased. The surface area of inunction has only a slight influence on the T levels achieved. The gels permit an easy adaptation of the dose to the individual needs.

Other T formulations, such as bio-degradable T microspheres (181) or cyclodextrin complexed sublingual formulations (182, 183) are under experimentation.

Monitoring androgen supplementation. During treatment, the eventual development of side effects should be carefully monitored by 6 monthly rectal examinations of the prostate, PSA, and hematocrit and plasma lipid determinations. Any increase of PSA by more than 0.75 ng/ml in two consecutive controls or a PSA level abnormal for age (>4 ng/ml) (184) requires further examination and eventually biopsy, whereas any increase of the hematocrite above 51% requires reduction of the dose or temporarily arrest of the treatment.

Further developments

A major problem in the evaluation of the need of androgen supplementation is the absence of clinically useful biological parameters of androgen action, which would enable more exact evaluation of the androgen requirements of elderly men. Such parameters are urgently needed to identify objectively elderly men in need of androgen supplementation.

The biological effects of T are mediated by T itself (in muscle for example), by its 5α reduced metabolite, dihydrotestosterone, formed locally in target tissues (skin, external genitalia, and prostate) and by estradiol (bone and central nervous system). Local formation of DHT will stimulate prostatic growth and eventually prostatic carcinoma. Hence more organ selective androgens, specific AR modulators (SARMS) (185), with a desired profile of activity, stimulating only the desired organs (for example bone) without affecting other organs, would be a useful addition to our therapeutic arsenal. 17α methyl-19-nortestosterone, which does not undergo 5α reduction but does undergo aromatization and appears to be 10 times as active as T at the feed back, but only twice at the prostate level, is the first of such SARMS (186, 187) to provide adequate replacement in hypogonadal men (188). The existence of 2 forms of AR (AR-A and AR-B) (189) with different tissue distribution might contribute to the development of other SARMS.

Finally, we urgently need more carefully designed, well controlled, long-term, large-scale studies of HRT in healthy elderly men with subnormal T levels. These should permit an objective balance between the benefits and risks of HRT and, eventually, permit a wider application of HRT in elderly men.

General conclusions

Aging is unavoidable and physiologic, but the large interindividual disparity in the pace of development and progression of signs and symptoms of aging, suggests that the development of this symptomatology can be delayed and that a high quality of life can be maintained until a very advanced age, in other words that it is possible to add life to years. Being aware of these possibilities, more and more elderly men (and women) will seek medical help to achieve these goals.

Many signs and symptoms of aging in males are reminiscent of the symptoms of young hypogonadal men. These symptoms are often significantly (albeit often weakly) correlated with T levels. Therefore, although these symptoms have a complex origin it may be reasonably assumed that the age-associated decrease in T levels is in part responsible for these symptoms. As shown in almost all studies, androgen supplementation in elderly men with subnormal T levels, has favorable, albeit often modest, effects on most of the symptoms, such as muscle mass and strength, fat mass, BMD, mood and general well-being. Therefore, it seems logical to consider that in elderly men with subnormal T levels and clinical symptoms suggestive of androgen deficiency, hormone replacement therapy in combination with physical activity (resistance training) and adequate nutrition will result in an optimal increase in muscle strength, BMD, and general sense of well-being.

However, data on clinical effects of androgen substitution, such as cardiovascular morbidity and mortality, falls and bone fracture rates are so far not available.

The major contraindication for androgen supplementation is the presence of a prostatic carcinoma.

Whereas interest in androgen supplementation in the aging male is certainly increasing, the number of controlled studies as well as the number of patients involved, remains disappointingly low, and available data are too limited to permit a definitive balance between risks and benefits. Hence, we cannot recommend routine androgen supplementation in elderly men and this treatment should still be limited to patients with both symptoms suggestive of androgen deficiency and with subnormal T levels, after careful exclusion of contraindications.

The promising results obtained so far may nevertheless raise the hope that, when more research will have been performed, it will be possible to define accurately the indications for androgen supplementation and identify the elderly to profit most of the treatment. Hormonal therapy then, together with adequate physical activity and a healthy life style might delay the aging process, prevent disability, and contribute to maintain the elderly as well integrated members of society and enable them to enjoy the highest quality of life.

References

1. Tenover JS. 1992 Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab.* 75:1092–1098.
2. Morley JE, Perry HM, Kaiser FE, et al. 1993 Effect of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geriatr Soc.* 41:149–152.
3. Bremner WJ, Vitiello WV, Prinz PN. 1983 Loss of circadian rhythmicity in blood testosterone levels with aging. *J Clin Endocrinol Metab.* 51:1278–1281.
4. Kaufman JM, Vermeulen A. 1998 Androgens in male senescence. In: Nieschlag E, Behre HM, eds. *Testosterone, Action, Deficiency, Substitution.* Springer; 437–471.
5. Morley JE, Kaiser FE, Perry HM, et al. 1997 Longitudinal changes in testosterone, luteinizing hormone and follicle stimulating hormone in healthy old men. *Metabolism.* 46:410–413.
6. Pearson UJD, Blackman MR, Metter EJ, Waclawiw Z, Carter HB, Herman JM. Effect of age and cigarette smoking on longitudinal changes in androgens and SHBG in healthy males. *Proc 77th Meeting of The Endocrine Soc., Washington, DC, 1995, p 322 (Abstract).*
7. Krithivas K, Yurgalevitch SM, Mohr BA, et al. 1999 Evidence that the CAG repeat in the androgen receptor is associated with age related decline in serum androgens levels in men. *J Endocrinol.* 162:137–142.
8. Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH. 1997 Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle age men: a 13 year follow-up of former Multiple Risk Factors Intervention Trial participants. *Am J Epidemiol.* 46:609–617.
9. Harman ME, Metter J, Toben JD, Pearson J, Blackman MR. 2000 Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab.* 86:724–731.
10. Turner HE, Wass JAH. 1997 Gonadal function in men with chronic illness. *Clin Endocrinology.* 47:379–403.
11. Vermeulen A, Kaufman JM, Giagulli VA. 1996 Influence of some biological indices on the sex hormone binding globulin and androgens in aging and obese men. *J Clin Endocrinol Metab.* 81:1821–1827.
12. Couillard C, Gagnon J, Bergeron F, et al. 2000 Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentration in men. The HERITAGE study. *J Clin Endocrinol Metab.* 85:1026–1031.
13. Rudman D, Drinka PJ, Wilson CR, et al. 1994 Relations of endogenous anabolic hormones and physical activity to bone mineral density and lean body mass in elderly men. *Clin Endocrinol.* 40:653–661.
14. Orwoll ES, Klein RF. 1995 Osteoporosis in men. *Endocr Rev.* 16:87–116.
15. Foresta G, Ruzza G, Mioni R, et al. 1984 Osteoporosis and decline of gonadal function in the elderly male. *Horm Res.* 19:18–22.
16. Center JR, Nguyen TV, Sambrook PN, Eisman JA. 1999 Hormonal and biochemical parameters in the determination of osteoporosis in elderly men. *J Clin Endocrinol Metab.* 84:3626–3635.
17. Murphy S, Khaw KT, Cassidy A, Compston E. 1993 Sex hormones and bone mineral density in elderly men. *Bone Miner.* 20:133–140.
18. Kaufman JM. 1996 Androgens, bone metabolism and osteoporosis. In: Odds B, Vermeulen A, eds. *Androgens and the Aging Male.* New York, London: Parthenon Publishing Group; 39–60.
19. Drinka PJ, Olson J, Bauwens S, Voeks SK, Carlson I, Wilson M. 1993 Lack of association between free testosterone and bone density separate from age in elderly males. *Calcif Tissue Int.* 52:67–69.
20. Meier DE, Orwoll ES, Keenan EJ, Fagerstrom RM. 1987 Marked decline of trabecular bone mineral content in healthy men with age: lack of association with sex steroid levels. *J Am Geriatr Soc.* 35:198–197.
21. Clarke BL, Ebeling PR, Jones JD, et al. 1996 Changes in quantitative bone histometry in aging healthy men. *J Clin Endocrinol Metab.* 81:2264–2270.
22. Greendale G, Edelstein S, Barrett-Connor E. 1997 Endogenous sex steroids and bone mineral density in older women and men. The Rancho Bernardo Study. *J Bone Miner Res.* 12:1833–1841.
23. Khosla S, Melton LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men: a key role for bio-available estrogen. *J Clin Endocrinol Metab.* 83:2266–2275.
24. van den Beld AW, de Jong FH, Grobbee DE, Pols HAP, Lamberts SWJ. 2000 Measures of bio-available serum testosterone and estradiol and their relationship with muscle strength, bone density and body composition in elderly men. *J Clin Endocrinol Metab.* 85:3276–3282.
25. Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J. 1997 Effect of testosterone and estradiol in a man with aromatase deficiency. *N Engl J Med.* 337:91–95.
26. Barrett-Connor E, Mueller JE, von Mühlen DG, Laughlin GA, Schneider DL, Sartoris DJ. 2000 Low levels of estradiol are associated with vertebral fractures in older men but not in women. The Rancho Bernardo Study. *J Clin Endocrinol Metab.* 85:219–223.
27. Vermeulen A, Goemaere S, Kaufman JM. 1999 Sex hormones, body composition and aging. *The Aging Male.* 2:8–15.
28. Seidell JC, Björntorp P, Sjöström L, Kvist H, Sannerstedt R. 1990 Visceral fat accumulation in men is positively associated with insulin, glucose and C-peptide levels, but negatively with testosterone levels. *Metabolism.* 39:897–901.
29. Tchernof A, Labrie F, Belanger A, et al. 1997 Relationships between endogenous sex steroid hormones, sex hormone binding globulin and lipoprotein levels in men: contribution of visceral obesity, insulin levels and other metabolic variables. *Atherosclerosis.* 133:235–244.
30. Kennell WB, Cupples LA, Ramaswani R, Stokes III J, Kreger BE, Higgins M. 1991 Regional obesity and risk of coronary disease. The Framingham Study. *J Clin Epidemiol.* 44:183–190.

31. Björntorp P. 1993 Visceral obesity: a civilisation syndrome. *Obes Res.* 1:206–222.
32. Larsson L. 1983 Histochemical characteristics of human skeletal muscle during aging. *Acta Physiol Scand.* 117:469–471.
33. Frontera WR, Hughes VV, Fiatarone MA, Fielding RA. 2000 Aging and skeletal muscle: a 12 year longitudinal study. *J Appl Physiol.* 88:1321–1326.
34. Reed RL, Pearlmuter L, Jochum K, Meredith KE, Mooradian AD. 1991 The relationship between muscle mass and muscle strength in the elderly. *J Am Geriatr Soc.* 39:555–591.
35. Abassi A, Drinka PJ, Mattson DE, Rudman D. 1993 Low circulating levels of insulin-like growth factors and testosterone in chronically institutionalized elderly men. *J Am Geriatr Soc.* 48:975–981.
36. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. 1999 Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev.* 107:123–136.
37. Verhaar HJJ, Samson MM, Aleman A, de Vries WR, de Vreede PL, Koppeschaar HPF. 2000 The relationship between indices of muscle function and circulating anabolic hormones in healthy. *The Aging Male.* 3:75–80.
38. Kirkland RT, Keenan BS, Probstfield JL, Patsch W, Tsai-Lien L, Clayton WJ, Insull Jr W. 1987 Decrease in plasma high density lipoprotein cholesterol at puberty in boys with delayed adolescence. Correlation with plasma testosterone levels. *JAMA.* 27:502–507.
39. Barrett-Connor E, Khaw RT, Yen SS. 1995 Testosterone and risk factors for cardiovascular disease in men. *Diabetes Metab.* 21:156–161.
40. Bagatell CS, Bremner WJ. 1995 Androgen and progestogen effects on plasma lipids. *Prog Cardiovasc Dis.* 38:255–271.
41. Haffner JM. 1996 Androgens in relation to cardiovascular disease and insulin resistance in aging men. In: Oddens B, Vermeulen A, eds. *Androgens and the Aging Male.* New York, London: Parthenon Publishing Group; 65–84.
42. Caron P, Bennet A, Camare L, Louvet JP, Boneu S, Sie P. 1989 Plasminogen activator inhibitor in plasma is related to testosterone in man. *Metabolism.* 38:1010–1013.
43. Phillips G, Pinkernell BH, Jing TY. 1994 The association between hypotestosteronemia and coronary heart disease in men. *Arterioscler Thromb.* 14:701–706.
44. Swartz CA, Young MA. 1987 Low serum testosterone and myocardial infarction in geriatric male inpatients. *J Am Geriatr Soc.* 35:39–44.
45. Haffner JE, Moss SE, Klein BEK, Klein R. 1996 Sex hormones and DHEASO4 in relation to ischemic heart disease in diabetic subjects. *The WESDR Study Diabetes Care.* 19:1045–1050.
46. Barrett-Connor E, Khaw KS. 1988 Endogenous sex hormone levels and cardiovascular disease in men: a prospective population based study. *Circulation.* 78:539–543.
47. Cauley JA, Gutai JP, Kuller LH, Dai WS. 1987 Usefulness of sex steroid hormone levels in predicting coronary artery disease in men. *Am J Cardiol.* 60:771–777.
48. Goldberg RB, Rabin AN, Alexander AN, Doelle GC, Getz GS. 1985 Suppression of plasma testosterone leads to an increase in serum total and high density lipoprotein cholesterol and Apo A and B. *J Clin Endocrinol Metab.* 60:203–207.
49. Moorjani S, Dupont A, Labrie F, et al. 1987 Increase in plasma high density lipoprotein concentration following complete androgen blockade in men with prostatic carcinoma. *Metabolism.* 36:244–250.
50. Polderman KH, Stehouwer CDA, van de Kamp GJ, Dekker GH, Verheugt FWA, Gooren LJG. 1993 Influence of sex hormones on plasma endothelin levels. *Ann Intern Med.* 118:429–431.
51. Ajayi AA. 1995 Testosterone increases platelet thromboxane A₂ receptor density. *Circulation.* 91:2740–2747.
52. Kannell WB, Cupples LA, Ramaswami R, Stokes Jr J, Kreger BE, Higgings M. 1991 Regional obesity and the risk of coronary disease: The Framingham Study. *J Clin Epidemiol.* 44:183–190.
53. Schiavi RC. 1996 Androgens and sexual function in men. In: Oddens B, Vermeulen A, eds. *Androgens and the Aging Male.* New York, London: Parthenon Publishing Group; 111–128.
54. Schiavi RC, Schreiner-Engel P, White D, Mandeli J. 1988 Pituitary-gonadal function during sleep in men with hypoactive sexual desire and in normal controls. *Psychosomat Med.* 50:304–318.
55. Pfeilschifter J, Scheidt-Nave C, Leidig-Bruckner G, et al. 1996 Relationship between circulating insulin-like growth factor components and sex hormones in population based sample of 50–80 year old men and women. *J Clin Endocrinol Metab.* 81:2534–2540.
56. Nilsson P, Moller L, Solkad K. 1995 Adverse effects of psychosocial stress on gonadal function and insulin levels in middle aged males. *J Intern Med.* 237:479–486.
57. Buena F, Swerdloff RS, Steiner BC, et al. 1993 Sexual function does not change when serum testosterone levels are varied pharmacologically within the normal male range. *Fertil Steril.* 59:1118–1123.
58. Kraemer HC, Becker HB, Brodie HH, Doering CH, Moos RH, Hamburg DA. 1976 Orgasmic frequency and testosterone levels in normal human males. *Arch Sex Behav.* 5:125–128.
59. Bancroft J. 1984 Androgens, sexuality and the aging male. In: Labrie F, Proulx L, eds. *Endocrinology.* Amsterdam: Elsevier; 913–916.
60. Mills TM, Reilly CM, Lewis RW. 1996 Androgens and penile erection. A review. *J Andrology.* 17:633–638.
61. Lugg J, Rafferty J, Gonzales-Cadavit NF. 1995 Dihydrotestosterone is the active androgen in the maintenance of nitric-oxide mediated penile erection in the rat. *Endocrinology.* 136:1495–1501.
62. Carani C, Scuberi A, Marrama P, Bancroft J. 1990 Effect of testosterone administration and visual erotic stimuli on nocturnal penile tumescence. *Horm Behav.* 24:435–441.
63. Davidson JM, Kwan M, Greenleaf WJ. 1982 Hormonal replacement therapy and sexuality. *Clin Endocrinol Metab.* 11:599–623.
64. Christiansen K, Kussmann R. 1987 Sex hormones and cognitive functions in men. *Neuropsychobiology.* 18:27–36.
65. McKeever WF, Deyo A. 1990 Testosterone, dihydrotestosterone and spatial task performance of males. *Bull Psychonomic Soc.* 28:305–308.
66. Christiansen K. 1998 Behavioural correlates of testosterone. In: Nieschlag E, Behre HM, eds. *Testosterone, Action, Deficiency, Substitution.* Springer; 107–142.
67. Barrett-Connor E, von Mühlen DG, Kritz-Silverstein D. 1999 Bio-available testosterone and depressive mood in older men. *The Rancho-Bernardo Study.* *J Clin Endocrinol Metab.* 84:573–577.
68. Martin FC, Yeo AL, Sonksen PA. 1997 Growth hormone secretion in elderly men: aging and the somatopause. *Baillière's Clin Endocrinol Metab.* 11:213–220.
69. Orentreich N, Brind JL, Rizer RL, Vogelmann JM. 1984 Age changes and sex difference in serum dihydroepiandrosterone sulfate concentration during adulthood. *J Clin Endocrinol Metab.* 59:551–555.
70. Zumoff B, Rosenfeld RS, Strain W, Levin J, Fukushima DK. 1980 Sex differences in the twenty four hour plasma concentration of dehydroisoandrosterone (DHA) and dehydroisoandrosterone sulfate (DHAS) in normal adults. *J Clin Endocrinol Metab.* 51:330–333.
71. Laughlin CA, Barrett-Connor E. 2000 Sexual dimorphism in the influence of advancing age on adrenal hormone levels: The Rancho Bernardo Study. *J Clin Endocrinol Metab.* 85:3561–3568.
72. Ravaglia G, Forti P, Maioli F, et al. 1996 The relationship of dehydroepiandrosterone sulfate (DHEAS) to endocrine metabolic parameters and functional status in the oldest old. Results from an Italian study on healthy free living over ninety years old. *J Clin Endocrinol Metab.* 81:1373–1378.
73. Abassi A, Duthie Jr EH, Sheldahl L, et al. 1998 Association of dehydroepiandrosterone sulfate, body composition and physical fitness in independent community dwelling older men. *J Am Geriatr Soc.* 46:263–273.
74. Barrett-Connor E, Khaw KT, Yen SCC. 1986 A prospective study of dehydroepiandrosterone sulfate: morbidity and cardiovascular disease. *N Engl J Med.* 315:1519–1524.
75. Berr C, Lafont S, Debuire B, Dartigues JF, Baulieu EE. 1996 Relationship of dehydroepiandrosterone sulfate in the elderly with functional, psychological and mental status and short term mortality. A French community based study. *Proc Natl Acad Sc USA.* 93:13410–13415.
76. Barrett-Connor E, Goodman-Gruen D. 1995 The epidemiology of DHEAS and cardiovascular disease. *Ann NY Acad Sci.* 774:259–270.
77. Lacroix AZ, Katzuhiko Y, Reed DM. 1992 Dehydroepiandrosterone sulfate, incidence of myocardial infarction and extend of atherosclerosis in men. *Circulation.* 86:1929–1935.
78. Morales AJ, Haubicht RH, Hwang JY, Asakura H, Yen SS. 1998 The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age advanced men and women. *Clin Endocrinol.* 49:421–432.
79. Flynn AMA, Weaver-Osterholz D, Sharpe-Timms KL, Krause G. 1999 Dehydroepiandrosterone in aging humans. *J Clin Endocrinol Metab.* 84:1527–1533.
80. Arlt W, Callies F, van Vlijmen JC, et al. 1999 Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med.* 341:1013–1020.
81. Hunt PJ, Gurnell EM, Huppert FA, et al. 2000 Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab.* 85:4650–4656.
82. Vermeulen A, Kaufman JM. 1995 Aging and the hypothalamo-pituitary testicular axis in men. *Horm Res.* 43:25–28.
83. Winters J, Sherins RJ, Troen P. 1984 The gonadotropin repressive activity of androgens is increased in elderly men. *Metabolism.* 33:1052–1059.
84. Deslypere JP, Kaufman JM, Vermeulen T, Vogelaers D, Vandalem JL, Vermeulen A. 1987 Influence of age on pulsatile luteinizing hormone release and responsiveness of the gonadotrophs to sex hormone feed-back. *J Clin Endocrinol Metab.* 64:68–73.
85. Winters SJ, Atkinson L, for the Testoderm Study Group. 1997 Serum LH concentration in hypogonadal men during transdermal testosterone replacement through scrotal skin: further evidence that aging enhances testosterone negative feed back. *Clin Endocrinol.* 47:317–322.
86. Rajfer JK, Namkun PC, Petra PH. 1989 Identification, partial characterization of age associated changes in a cytoplasmic androgen receptor in the rat penis. *J Steril Biochem.* 33:1689–1392.
87. Gonzales-Cadavit NF, Swerdloff RS, Lemmi CAE, Rafferty J. 1991 Expression

- of androgen receptor gene in rat penile tissue and cells during sexual maturation. *Endocrinology*. 129:1671–1678.
88. Roehrborn CG, Lange JL, George FW, Wilson JD. 1987 Changes in amount and intracellular distribution of androgen receptor in human foreskin as a function of age. *J Endocrinol*. 79:44–47.
 89. Toghi H, Utsugisawa K, Yamagata M, Yoshimura M. 1995 Effects of age on messenger RNA expression of glucocorticoid, thyroid hormone, androgen and estrogen receptor in postmortem human hippocampus. *Brain Res*. 700:245–253.
 90. Ono K, Haji M, Nawata H, Maki T, Kato KI, Ibayashi H. 1988 Age related changes in glucocorticoid and androgen receptors of cultured human skin fibroblasts. *Gerontology*. 34:128–133.
 91. Greenstein BD. 1979 Androgen receptors in the rat brain, anterior pituitary gland and ventral prostate: effects of orchietomy and aging. *J Endocrinol*. 81:75–81.
 92. Mowsowicz I, Riahi M, Wright F, Bouchard P, Kuttent F, Mauvais-Jarvis P. 1981 Androgen receptor in human skin cytosol. *J Clin Endocrinol Metab*. 52:338–344.
 93. Fishman HR, Nyberg LM, Bujnovsky P, Brown TR, Walsh PC. 1981 The ontogeny of the androgen receptor in human foreskin. *J Clin Endocrinol Metab*. 52:919–923.
 94. Bagatell C, Heiman JR, Rivier RE, Bremner WJ. 1994 Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. *J Clin Endocrinol Metab*. 78:711–716.
 95. Anderson DC. 1974 Sex hormone binding globulin. *Clin Endocrinol*. 3:69–96.
 96. Vermeulen A, Verdonck L, Kaufman JM. 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*. 84:3666–3672.
 97. Snyder PJ, Peachy H, Hannoush P, et al. 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab*. 84:2647–2653.
 98. Wang C, Swerdloff RS, Iranmanesh A, et al. 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*. 85:2839–2853.
 99. Brodsky IG, Balagopal P, Nair KS. 1996 Effects of testosterone replacement therapy on muscle mass and muscle protein synthesis in hypogonadal men. *J Clin Endocrinol Metab*. 81:3469–3477.
 100. Behre HM, von Eckhardstein S, Kliesch S, Nieschlag E. 1999 Long term substitution of hypogonadal men with transscrotal testosterone over 7–10 years. *Clin Endocrinol*. 50:629–635.
 101. Wang C, Eyre DE, Clark R, et al. 1996 Sublingual testosterone replacement improves muscle mass and strength, decreases bone resorption and increases bone formation in hypogonadal men. *J Clin Endocrinol Metab*. 81:3654–3662.
 102. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klinbanski A. 1996 Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab*. 81:4358–4365.
 103. Snyder PJ, Peachey H, Berlin JA, et al. 2000 Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab*. 85:2670–2677.
 104. Bhasin S, Storer TW, Berman N, et al. 1997 Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J Clin Endocrinol Metab*. 82:407–413.
 105. Sheffield-Moore M, Urban RJ, Wolf SE, et al. 1999 Short-term oxandrolone administration simulates net muscle protein synthesis in young men. *J Clin Endocrinol Metab*. 84:2705–2711.
 106. Urban RJ, Bodenburger C, Gilkison C, et al. 1995 Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol*. 269:E820–E826.
 107. Urban RJ, Gilkison C, Jiang J, et al. Testosterone administration to older men for 6 months increases skeletal muscle strength, net muscle protein balance and the expression of intramuscular IgF-1 transcription. *Proc 82nd Meeting of The Endocrine Soc.*, 2000, p 393 (Abstract).
 108. Sih R, Morley JE, Kaiser FE, Perry III HM, Patrick P, Ross C. 1997 Testosterone replacement in older hypogonadal men: a 12 months randomized controlled study. *J Clin Endocrinol Metab*. 82:1661–1667.
 109. Tenover JS. 1994 Androgen administration in aging men. *Endocrinol Metab Clin*. 23:877–889.
 110. Clague JE, Wu FC, Horan MA. 1999 Difficulties in measuring the effect of replacement therapy on muscle function in old age. *Int J Androl*. 22:261–267.
 111. Bhasin S, Bagatell CJ, Bremner WJ, et al. 1998 Therapeutic perspective: Issues in testosterone replacement in older men. *J Clin Endocrinol Metab*. 83:3435–3548.
 112. Behre HH, Kliesch S, Leifke E, Link TM, Nieschlag E. 1997 Long term effect of testosterone therapy on bone mineral density in hypogonadal men. *J Clin Endocrinol Metab*. 82:2386–2390.
 113. Saggese G, Bertelloni S, Baroncelli GI. 1997 Sex steroids and acquisition of bone mass. *Horm Res*. 48:65–72.
 114. Anderson FH, Francis RM, Faulkner K. 1996 Androgen supplementation in eugonadal men with osteoporosis. Effects of 6 months of treatment on bone mineral density and cardiovascular risk factors. *Bone*. 18:171–178.
 115. Snyder PJ, Peachey H, Hannoush P, et al. 1999 Effects of testosterone treatment on bone mineral density in men over 65 years old. *J Clin Endocrinol Metab*. 84:1966–1972.
 116. Vanderschueren D, Vandeput L, Boonen S, Van Herck E, Swinnen JV, Bouillon R. 2000 An aged rat model of partial androgen deficiency: prevention of both loss of bone and lean body mass by low dose androgen replacement. *Endocrinology*. 141:1642–1647.
 117. Peacock M, Liu M, Carly M, et al. 2000 Effect of calcium or 25 OH vit D₃ dietary supplementation in bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab*. 85:3011–3019.
 118. Bagatell CJ, Heiman J, Matsumoto AM, Rivier JE, Bremner WJ. 1994 Metabolic and behavioral effects of high dose exogenous testosterone. *J Clin Endocrinol Metab*. 79:561–567.
 119. Anderson RA, Bancroft J, Wu FCW. 1992 The effects of exogenous testosterone on sexuality and mood of normal men. *J Clin Endocrinol Metab*. 75:1503–1507.
 120. Hajjar RR, Kaiser FE, Morley JE. 1997 Outcomes of long-term testosterone replacement therapy in older hypogonadal males: a retrospective study. *J Clin Endocrinol Metab*. 82:3793–3796.
 121. Wang C, Swerdloff R, Iranmanesh A, et al. 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*. 85:2839–2953.
 122. Carani C, Rochira V, Faustini-Fustini M, Balestrieri A, Granata ARM. 2000 Role of oestrogen in male sexual behaviour: insights from the natural model of aromatase deficiency. *Clin Endocrinol*. 51:517–524.
 123. Wang C, Alexander G, Berman N, et al. 1996 Testosterone replacement therapy improves mood in hypogonadal men. *J Clin Endocrinol Metab*. 81:3578–2383.
 124. Marin P, Holmäng S, Gustafson C, et al. 1993 Androgen treatment of abdominally obese men. *Obesity Res*. 1:245–248.
 125. Ellyin FM. The long term beneficial effect of low dose testosterone in the aging male. *Proc 77th Meeting of The Endocrine Soc.*, Washington, DC, 1995, pp 2–127 (Abstract).
 126. Orwoll ES, Oviatt SK, Biddle J, et al. Transdermal testosterone supplementation in normal older men. *Proc 74th Meeting of The Endocrine Soc.*, San Antonio, TX, 1992, p 319.
 127. Alexander GM, Swerdloff RS, Wang C, et al. 1998 Androgen-behavior correlations in hypogonadal men and eugonadal men. *Horm Behav*. 33:85–94.
 128. Janowski SC, Oviatt SK, Orwoll ES. 1994 Testosterone influences spatial cognition in older men. *Behav Neurosci*. 108:325–332.
 129. Asscheman H, Gooren LJG, Megens JAJ, Nauta J, Kloosterboer HJ, Eikelboom LJG. 1994 Serum testosterone is the major determinant of male-female differences in serum level of high-density lipoprotein cholesterol and HDL-2 cholesterol. *Metabolism*. 43:935–939.
 130. Wu FCW, Farley TMM, Peregoudov A, Waites GHM, World Health Organization Task Force for the Regulation of Male Fertility. 1996 Effect of exogenous testosterone in normal men. Experience from a multicenter efficacy study using testosterone-enanthate. *Fertil Steril*. 65:626–636.
 131. Anderson RA, Wallace BM, Wu FCW. 1995 Effects of testosterone enanthate on serum lipoproteins in man. *Contraception*. 52:115–119.
 132. Berglund L, Carlström K, Stege R, et al. 1996 Hormonal regulation of serum lipoprotein(a) levels: effect of parenteral administration of estrogen or testosterone in males. *J Clin Endocrinol Metab*. 81:2633–2637.
 133. Tenover JL. 1996 Effects of androgen supplementation in aging males. In: Oddsens B, Vermeulen A, eds. *Androgens and the Aging Male*. New York, London: Parthenon Publishing Group; 191–204.
 134. Handa K, Ischii H, Kono S, et al. 1997 Behavioral correlation of plasma sex hormones and their relationship with plasma lipids and lipoproteins in Japanese men. *Atherosclerosis*. 130:37–44.
 135. Simon D, Charles MA, Nahoul K, et al. 1996 Androgen therapy improves insulin sensitivity in healthy men with low plasma testosterone. *Diabetes*. 45(Suppl 2):856.
 136. Kenny AM, Prestwood KM, Marcello KD, Fall PM, Raisz LC. 2000 The effects of transdermal testosterone on bone metabolism, body composition, lipids and health related quality of life in older men. *The Aging Male* 3:3 (Abstract).
 137. Münzer T, Harman SM, Christmas C, et al. 2000 Effects of administration of testosterone and/or GH in healthy aged men. *The Aging Male* 3:3 (Abstract).
 138. Marin P, Lonn B, Andersson B, Oden B, Olbe L, Bengtsson BA. 1996 Assimilation of triglycerides in subcutaneous and intra-abdominal adipose tissues *in vivo* in men. *J Clin Endocrinol Metab*. 81:1018–1022.
 139. Xu X, De Pergola G, Björntorp P. 1991 Testosterone increases lipolysis and the number β -adrenoreceptors in male rat adipocytes. *Endocrinology* 128:379–381.
 140. Marin P, Oden B, Björntorp P. 1995 Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue *in vivo* in men: effects of androgens. *J Clin Endocrinol Metab*. 80:239–243.
 141. Alexandersen P, Haarlo J, Christiansen C. 1996 The relationship of natural androgens to coronary heart disease in males. *Atherosclerosis* 125:1–13.
 142. Bonithon-Kopp C, Scarabin PY, Bara L, Castanier M, Jacqueson A, Roger M. 1998 Relationship between sex hormones and haemostatic factors in healthy middle aged men. *Atherosclerosis*. 71:71–76.
 143. Glueck CJ, Glueck HI, Stroop D, Speirs J, Hamer T, Tracy T. 1993 Endog-

- enous testosterone, fibrinolysis and coronary heart disease risk in hyperlipemic men. *J Lab Clin Med.* 122:412–420.
144. **Webb CM, McNeill JG, Hayward CS, Zeegler D, Collins P.** 1999 Effect of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation.* 100:1690–1693.
 145. **Rosano GM, Leonardo F, Pagnotta P, et al.** 1999 Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation.* 99:166–1670.
 146. **Ong PSL, Patrizi G, Chong WCF, Webb CM, Hayward CS, Collins P.** 2000 Testosterone enhances flow mediated brachial artery reactivity in men with coronary artery disease. *Am J Cardiol.* 85:14–17.
 147. **Webb CM, Adamson DL, de Ziegler D, Collins P.** 1999 Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *Am J Cardiol.* 83:1906–1911.
 148. **English KM, Steeds RP, Jones TH, Diver MJ, Channer KS.** 2000 Low dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a double blind placebo controlled study. *Circulation.* 102:1906–1911.
 149. **Bhasin S, Storer TW, Berman N, et al.** 1997 The effects of supraphysiological doses of testosterone on muscle size and strength in normal men. *N Engl J Med.* 335:1–7.
 150. **Young NR, Baker HWG, Lin G, Seeman E.** 1993 Body composition and muscle strength in healthy men receiving testosterone enanthate for contraception. *J Clin Endocrinol Metab.* 77:1028–1032.
 151. **Holmång S, Marin P, Lindstedt G, Hedelin H.** 1993 Effect of long-term oral testosterone-undecanoate treatment on prostatic volume and serum prostate specific antigen in eugonadal middle-aged men. *Prostate.* 23:99–106.
 152. **Behre HM, Bohmeyer J, Nieschlag E.** 1994 Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age matched normal controls. *Clin Endocrinology.* 40:341–349.
 153. **Hoffman MA, Morgantaler A, Dewolf WC.** 1999 Free and total testosterone in the evaluation of prostate cancer: does low free testosterone predisposes to more aggressive disease. *J Urol.* 161:321 (Abstract).
 154. **Kleinman KJP, McKinlay JB.** 2000 Prostate cancer: how much do we know and how do we know it? *The Aging Male.* 3:115–123.
 155. **Hardy DO, Scher HI, Bogenreider T, et al.** 1996 Androgen receptor CAG repeat length in prostate cancer: correlation with age of onset. *J Clin Endocrinol Metab.* 81:4400–4405.
 156. **Carter HB, Pearson JD, Metter EJ, et al.** 1995 Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate.* 27:25–31.
 157. **Gann PH, Hennekens CH, Longcope C, Stampfer MJ.** 1996 Prospective study of sex hormone levels and risk of prostatic cancer. *J Natl Cancer Inst.* 88:1118–1126.
 158. **Breslow N, Chan CW, Dhom G, et al.** 1977 Latent carcinoma of the prostate at autopsy in seven areas. *Int J Cancer.* 20:680–688.
 159. **de Jong FH, Oishi K, Hayes RB, et al.** 1991 Peripheral hormone levels in controls and in patients with prostatic cancer or benign prostatic hyperplasia: results from the Dutch-Japanese case control study. *Cancer Res.* 51:3445–3450.
 160. **Santner SJ, Albertson B, Zhang GY, et al.** 1998 Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. *J Clin Endocrinol Metab.* 83:2104–2109.
 161. **Schröder FH.** 1996 The prostate and androgens: the risk of supplementation. In: Oddens B, Vermeulen A, eds. *Androgens and the Aging Male.* New York, London: Parthenon Publishing Group; 223–231.
 162. **Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA.** 1999 Pharmacokinetics, efficiency and safety of a permeation enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone-*enanthate* for the treatment of hypogonadal men. *J Clin Endocrinol Metab.* 84:3469–3478.
 163. **Matsumoto AM, Sandblom RE, Schoene RB, et al.** 1985 Testosterone replacement in hypogonadal men: effect on obstructive sleep apnea, respiratory drives and sleep. *Clin Endocrinol Metab.* 22:713–721.
 164. **Santamaria JD, Prior SC, Fleetham JA.** 1988 Reversible reproductive dysfunction in men with obstructive sleep apnea. *Clin Endocrinology.* 28:461–470.
 165. **Gooren LJG.** 1994 A ten year safety study of the oral androgen, testosterone-undecanoate. *J Androl.* 15:212–215.
 166. **WHO, Nieschlag E, Wang C, et al.** 1992 Guidelines for the use of androgens WHO. Geneva: WHO.
 167. **Davidson DW, O'Carroll RO, Bancroft J.** 1987 Increasing circulating androgens with testosterone-undecanoate in eugonadal men. *J Steril Biochem.* 26:713–716.
 168. **Nieschlag E, Cuppers HJ, Wiegmann W, Wickings ES.** 1976 Bioavailability and LH suppressive effects of different testosterone preparations in normal and hypogonadal men. *Horm Res.* 7:134–141.
 169. **Zhang Gy, Gu Yq, Wang XH, Cui YG, Bremner WJ.** 1998 A pharmacokinetic study of injectable testosterone-undecanoate in hypogonadal men. *J Androl.* 19:761–768.
 170. **Jockenhövel F, Vogel E, Kreutzer M, Reinhard W, Lederbogen Reinwein D.** 1996 Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal en. *Clin Endocrinol.* 45:61–72.
 171. **Handelsman D, Mackey MA, Howe C, Turner L, Conway AJ.** 1997 An analysis of testosterone implants for androgen replacement therapy. *Clin Endocrinol.* 47:311–316.
 172. **Kelleher S, Turner L, Howe C, Conwang AJ, Handelsman DJ.** 2000 Extrusion of testosterone pellets: a randomized controlled clinical study. *Clin Endocrinol.* 51:469–472.
 173. **Bals-Pratsch M, Langer K, Place VA, Nieschlag E.** 1988 Substitution therapy of hypogonadal men with transdermal testosterone over one year. *Acta Endocrinol.* 118:7–13.
 174. **Findlay JC, Place V, Snyder PJ.** 1989 Treatment of primary hypogonadism in men with transdermal administration of testosterone. *J Clin Endocrinol Metab.* 68:369–373.
 175. **Meikle AW, Mazer NA, Moellmer JD, et al.** 1992 Enhanced transdermal delivery across non scrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. *J Clin Endocrinol Metab.* 74:623–628.
 176. **Vermeulen A, Deslypere JP.** 1985 Longterm transdermal dihydrotestosterone therapy: effects on pituitary gonadal axis and plasma lipoproteins. *Maturitas.* 7:281–287.
 177. **Wang C, Iranmanesh A, Berman V, et al.** 1998 Comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone gel in healthy elderly men. A clinical research center study. *J Clin Endocrinol Metab.* 83:2749–2757.
 178. **Swerdlow ES, Wang C.** 1998 Dihydrotestosterone: a rationale for the use of a non aromatizable androgen replacement therapeutic agent. *Baillière's Clin Endocrinol Metab.* 12:501–506.
 179. **Wang C, Berman C, Longstreth JA, et al.** 2000 Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site *versus* four sites. A general clinical research center study. *J Clin Endocrinol Metab.* 85:964–969.
 180. **Swerdlow RS, Wang C, Cunningham G, et al.** 2000 Long term pharmacokinetics of transdermal testosterone in hypogonadal men. *J Clin Endocrinol Metab.* 85:4500–4510.
 181. **Bhasin S, Swerdlow RS, Steiner BS, et al.** 1992 A biodegradable microsphere formulation provides uniform eugonadal levels of testosterone for 10–11 weeks in hypogonadal men. *J Clin Endocrinol Metab.* 74:75–83.
 182. **Salehian B, Wang C, Alexander G, et al.** 1995 Pharmacokinetics, bioefficacy and safety of sublingual testosterone cyclodextrin in hypogonadal men: a clinical research center study. *J Clin Endocrinol Metab.* 80:3567–3575.
 183. **Wang C, Eyre R, Clark R, et al.** 1996 Sublingual testosterone improves muscle mass and strength, decreases bone resorption and increases bone formation markers in hypogonadal men. A clinical research center study. *J Clin Endocrinol Metab.* 81:3654–3662.
 184. **Morgan TO, Jacobsen SJ, McCarty WF, Jacobsen DI, McLeod DG, Morel JW.** 1996 Age specific reference ranges for serum prostate specific antigen in black men. *N Engl J Med.* 335:304–310.
 185. **Negro-Villar A.** 1999 Selective androgen receptor modulators (SARMs): a novel approach to androgen therapy for the new millennium. *J Clin Endocrinol Metab.* 84:3559–3562.
 186. **Sundaram K, Kumar N, Bardin CW.** 1996 7 α methyl-19 nor-testosterone (MENT): an ideal androgen replacement therapy. In: Bhasin S, Gabelnick H, Spieler JM, Swerdlow RS, Wang C, eds. *Pharmacology, Biology and Clinical Applications of Androgens.* New York: Wiley-Liss; 493–497.
 187. **Anderson RA, Martin CW, King AWC, et al.** 1999 7 α methyl-19 nortestosterone maintains sexual behavior and mood in hypogonadal men. *J Clin Endocrinol Metab.* 84:3556–3562.
 188. **Anderson RA, Martin CW, Kung ACW, et al.** 1999 7 α methyl-19 nortestosterone (MENT) maintains sexual behavior and mood in hypogonadal men. *J Clin Endocrinol Metab.* 84:3556–3562.
 189. **Gao T, McPhaul MJ.** 1998 Functional activities of the A and B forms of the human androgen receptor agonists and antagonists. *Mol Endocrinol.* 12:654–663.