"MALE MENOPAUSE"

Department of Internal Medicine

Grand Rounds

December 3, 1992

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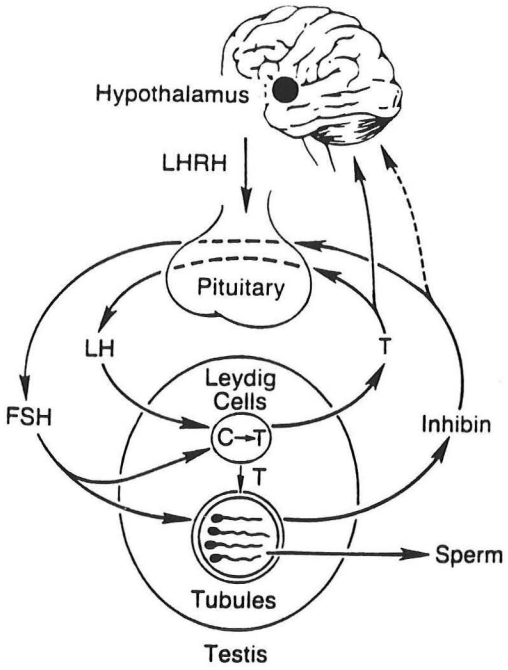
1. Does testicular function decrease with age?
2. Does male sexual function decrease with age?
3. Is hypogonadism or aging in men associated with decreased bone mass?
4. What effect does hypogonadism and/or aging in men have on lipoproteins?
5. Are there risks or benefits of androgen replacement therapy in elderly men with low testosterone?

In women there is a uniform predictable complete cessation of ovarian function at approximately age 50. Both gamete production and estrogen production by the ovary are lost, and the hypothalamus and pituitary respond appropriately with increases in both mean levels and pulse frequency of LH and FSH. These hormone changes are often associated with emotional changes, hot flashes, and altered sexual function with decreased vaginal lubrication. The rate of loss of bone mass increases following the menopause, and lipoprotein changes occur which are unfavorable for atherosclerotic events. Treatment of the postmenopausal woman with estrogens may be associated with an increased risk of endometrial cancer. However, hormone replacement therapy decreases the rate of loss of bone mass and improves the lipid profile decreasing atherosclerotic risk.

In these rounds I will review the evidence for a possible related series of events in elderly men. As we will see, the term "male menopause" or "male climacteric" is probably inappropriate because of the lack of timing of the changes in men with the usual age of menopause in women and the gradual rather than abrupt nature of changes that do occur in men.

Before discussing suspected abnormalities, the normal hypothalamic-pituitary-testicular axis should be considered (Fig. 1) (1). Pulsatile secretion of luteinizing hormone-releasing hormone (LHRH, also called gonadotropin-releasing hormone or GnRH) by hypothalamic neurons results in pulsatile secretion of LH and FSH by the anterior pituitary. LH stimulates Leydig cells to synthesize testosterone. FSH may play a role in steroidogenesis by influencing Leydig cell maturation. FSH primarily acts in the seminiferous tubules following binding to Sertoli cells by stimulating spermatogenesis in conjunction with androgen produced in adjacent Leydig cells. The rate of LH secretion is controlled by the action of sex steroids on the hypothalamus and pituitary. The control of LH in men operates primarily by negative feedback since normal levels of gonadal steroids inhibit secretion. Testosterone acts on the central nervous system to slow the hypothalamic pulse generator and consequently decrease the frequency of LH pulsatile release. Testosterone also appears to have a negative effect on LH secretion at the pituitary levels. The negative feedback inhibition of the testicular hormones on FSH secretion is less well understood. Serum FSH levels increase selectively in proportion to the loss of germinal elements in the testes. The peptide hormone inhibin is secreted by Sertoli cells, and this secretion is enhanced by FSH. Inhibin feeds back to block LHRH-stimulated FSH release. Whether inhibin also has effects at the hypothalamic level is not known. Testosterone and estradiol also have effects on FSH secretion.



Hypothalamic–pituitary–testicular interrelationships. Schematic diagram to indicate feedback relationship of testosterone and inhibin produced by testes on gonadotropin secretion by the hypothalamic–pituitary complex, and site of action of FSH and LH on testis. C, cholesterol; T, testosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LHRH, LH-releasing hormone.

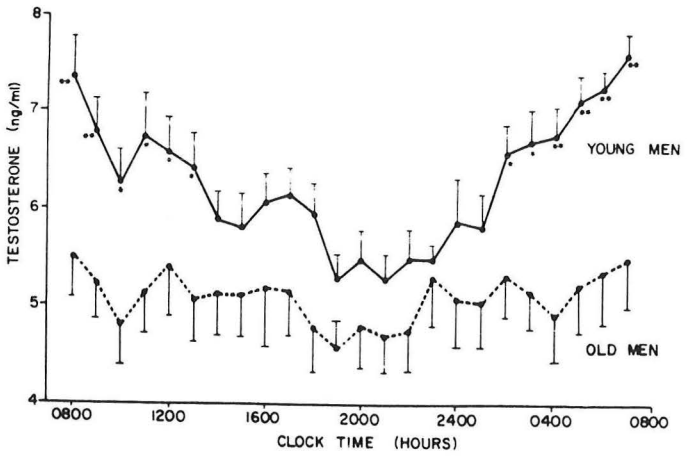
Figure 1

1. Griffin JE. Male reproductive function. In: Griffin JE and Ojeda SR, eds. Textbook of Endocrine Physiology, 2nd ed. Oxford, New York, 1992, pp 169-188.

I. Does Testicular Function Decline With Age?

A. Leydig Cell Function

The reports of serum testosterone in men of various ages initially appeared in the late 1940s (see Ref. 2 for early references). Most of the reports in the late 1960s and 1970s using radioimmunoassay consistently noted a decline in serum testosterone with age. However, most of these reports used data collected on hospitalized elderly or nursing home patients, subjects who might have illness related changes in gonadal function. In addition most of the earlier studies relied on single blood samples introducing potential sampling errors in not accounting for pulsatile secretion. Even when healthy men were examined in the early 1980s, some studies (3) could be faulted because of failing to recognize that there is some diurnal variation in serum testosterone with higher levels occurring in the morning in young men. Two studies with frequent sampling have clearly shown that a loss of the normal circadian rhythm of serum testosterone occurs in elderly men and that mean levels are lower in elderly men (4,5). The study with the most extensive sampling is that of Bremner and colleagues (4) in which hourly blood samples were obtained in 17 young (mean age 25.2 yr) and 12 old (mean age 71 yr) carefully screened healthy men. The men were nonsmokers, nonabusers of alcohol, and were receiving no medication. Moreover, normality was confirmed by complete history, physical exam, ECG, CBC, and urinalysis. Young men exhibited a clear circadian rhythm in serum testosterone levels with maximal levels at approximately 0800 h and minimal levels at 1900 to 2100 h (Fig. 2) (4). The elderly men had a circadian rhythm which was much less apparent.



Hourly serum testosterone levels (mean ± SEM) in normal young (n = 17) and old (n = 12) men. Blood samples were obtained using an indwelling peripheral venous cannula, which allowed free movement and normal sleep. *, $P < 0.05$; **, $P < 0.01$ (significance levels of the differences between young and old men at each time point). The *absence of an asterisk* denotes that there was no significant difference at that time point.

Figure 2

Deslypere and Vermeulen took an interesting approach to minimize possible differences in environmental factors by studying 71 monks living under identical conditions in a monastery (5). With several samples during the day the basic observations of Bremner and colleagues were confirmed. As in other careful studies of normal men, the decrease in serum testosterone levels in older men in these studies was to a level still within the range considered normal for young men.

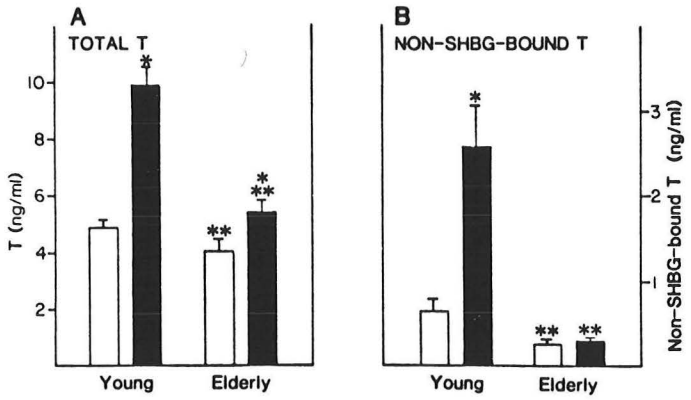
We now recognize that the fraction of circulating testosterone available for entry into target tissues is not only the free fraction as assessed by equilibrium dialysis but also that fraction loosely bound to albumin (6). Thus, many investigators have measured the non-sex hormone binding globulin (or non-SHBG)-bound testosterone as a measure circulating bioavailable testosterone. This fraction is the free plus albumin-bound testosterone and accounts for about 55% of the total testosterone on average. Since SHBG levels are known to increase in men with age, measuring only total testosterone might understate a decline in bioavailable testosterone. Two reports of bioavailable testosterone in young versus elderly men have confirmed a greater decrease in bioavailable testosterone than in total testosterone (Table I) (7,8). In the first report a single morning sample for total testosterone was used with no significant difference in total testosterone between young and elderly (7). In the second study 24 h mean values were determined based on sampling every 10 minutes. Note that in each study the percentage of total testosterone that was bioavailable was less in the elderly group than in the young group in keeping with the above mentioned increase in SHBG with age.

Table I. Total and Bioavailable Serum Testosterone in Young and Elderly Men

		Total	Bioavailable
Nankin and Calkins (Ref. 7)	young (n=13)	5.51 ± 0.7	2.46 ± 0.5
	elderly (n=7)	5.27 ± 1.7	1.58 ± 0.4*
Tenover et al (Ref. 8)	young (n=14)	4.90 ± 0.3	3.20 ± 0.2
	elderly (n=14)	4.10 ± 0.4*	1.90 ± 0.1*

Mean in ng/ml
*p < 0.05 or greater compared with young

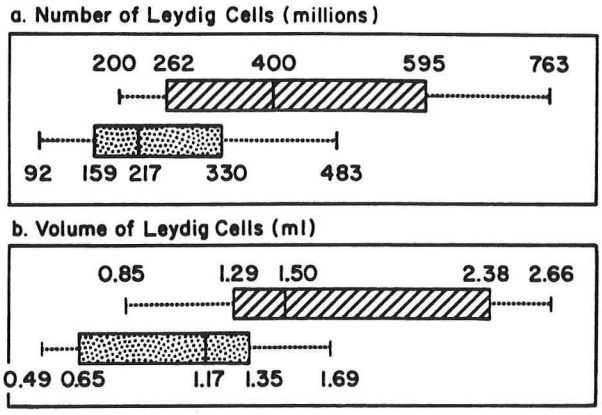
Leydig cell reserve can be tested by administering exogenous gonadotropins or stimulating LH secretion by an antiestrogen such as clomiphene citrate. The ability to increase serum testosterone in response to either type of stimulus is diminished in elderly men (3,7). The latter report with clomiphene administration found that in spite of similar LH response elderly men had a markedly blunted increase in mean 24-h total testosterone and no increase in bioavailable (or non-SHBG-bound) testosterone (Fig. 3) (8).



Mean (±SEM) 24-h serum total T levels (A) and calculated non-SHBG-bound T levels (B) in 14 young and 14 elderly men before (□) and after CC administration (■). *, $P < 0.01$ compared to baseline; **, $P < 0.05$ compared to young men (1 ng/mL total or non-SHBG-bound T = 3.5 nmol/L).

Figure 3

A sufficient explanation for the cause of decreased Leydig cell function with age is the fact that Leydig cells disappear from the adult human testis as a function of increasing age (Fig. 4) (9). The loss of Leydig cells is thought to be a result of degeneration and dissolution (10).

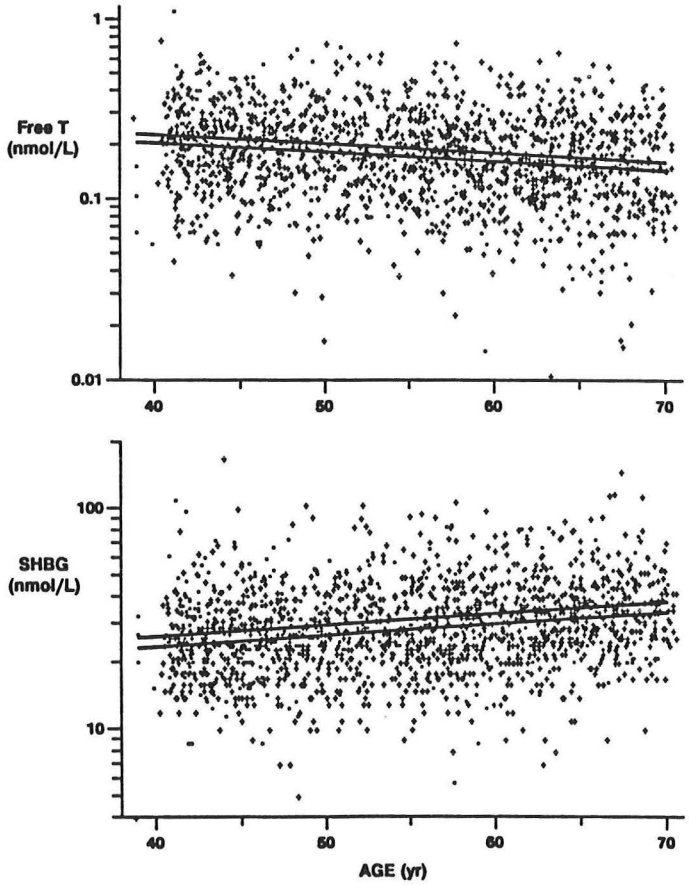


Comparison of numbers of Leydig cell nuclei (a), cytoplasm (b), serum LH These graphical representations of variation within groups of study subjects display minimum, 25th percentile, median, 75th percentile, and maximum values for each characteristic.

Figure 4

Thus far elderly men have been contrasted with young men in regard to Leydig cell function. When does this decline in Leydig cell function begin, and is it a relatively abrupt change as is the decline in ovarian function in women? The Massachusetts Male Aging Study has provided data on a large number of men in

a population-based cross-sectional survey of men aged 39-70 yr (11). Two groups were studied: Group 1 consisted of 415 men who were free of obesity, alcoholism, all prescription medication, prostate problems, and chronic illness (cancer, coronary heart disease, hypertension, diabetes, and ulcer). Group 2 consisted of 1294 men who reported one or more of the above conditions. Pooled morning samples were obtained for total, free, and albumin-bound testosterone and SHBG. The relationship of total, free and albumin-bound testosterone and SHBG with age was described by a constant percent change per year (1.2%/yr decline for free testosterone and 1.2%/yr increase for SHBG, note log-linear plot) (Fig. 5) (11). The age trends were parallel in Group 1 and Group 2 with Group 2 having 10-15% lower free testosterone and SHBG levels.



Opposing age trends of serum free testosterone (*above*) and SHBG (*below*) in 1709 Massachusetts males. Age trends were parallel in group 1 (●, healthy) and group 2 (+; reporting obesity, chronic illness, prescription medication, prostate problems, or excess alcohol consumption), with group 2 maintaining 10% lower serum concentration.

Figure 5

2. Tsitouras PD. Effects of age on testicular function. Endocrinol Metab Clin North Am 16:1045-1059, 1987

3. Harman SM, Tsitouras PD. Reproductive hormones in aging men. I. Measurements of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. J Clin Endocrinol Metab 51:35-40, 1980

4. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 56:1278-1281, 1983

5. Deslypere JP, Vermeulen A. Leydig cell function in normal men: Effect of age, lifestyle, residence, diet, and activity. J Clin Endocrinl Metab 59:955-962, 1984

6. Manni A, Pardridge WM, Cefalu W, Nisula BC, Bardin CW, Santner SJ, Santer RJ: Bioavailability of albumin-bound testosterone J Clin Endocrinol Metab 61:705-710, 1985

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8. Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metab 65:1118-1126, 1987

9. Neaves WB, Johnson L, Porter JC, Parker CR Jr., Petty CS. Leydig cell numbers, daily sperm production, and serum gonadotropin levels in aging men. J Clin Endocrinol Metab 59:756-763, 1984

10. Neaves WB, Johnson L, Petty CS. Age-related change in numbers of other interstitial cells in testes of adult men: evidence bearing on the fate of leydig cells lost with increasing age. Biol Reprod 33:259-269, 1985

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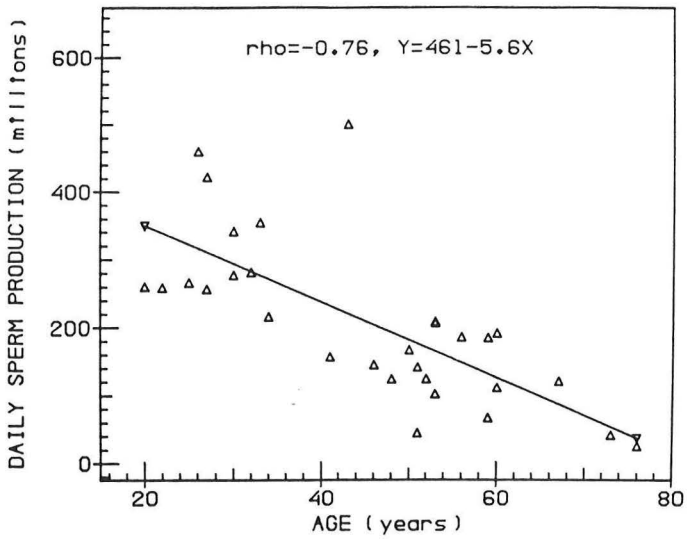
B. Seminiferous Tubule Function

Since normal seminiferous tubule function depends on testosterone production by the adjacent interstitial Leydig cells, one might anticipate that some decline in androgen production with age would be associated with defective spermatogenesis. Assessment of seminiferous tubule function by semen analysis in elderly men may be complicated by the decreased frequency of ejaculation with the associated increased total sperm counts and ejaculate volumes. None of the reported studies of ejaculates in elderly men assess a stable daily sperm output following depletion of extragonadal sperm reserves as described by Johnson et al (12). Another reliable method for quantitating sperm production is the measurement of daily sperm production (DSP) by the number of homogenization-resistant spermatids from biopsy material divided by the 2.9-day estimated life span of such spermatids (13). When daily sperm production determined by this method is studied as a function of age, there is a significent negative correlation with age ($p < 0.001$) (Fig. 6) (9). However, this decline in sperm output did not correlate with the number of Leydig cells in individual men (14).

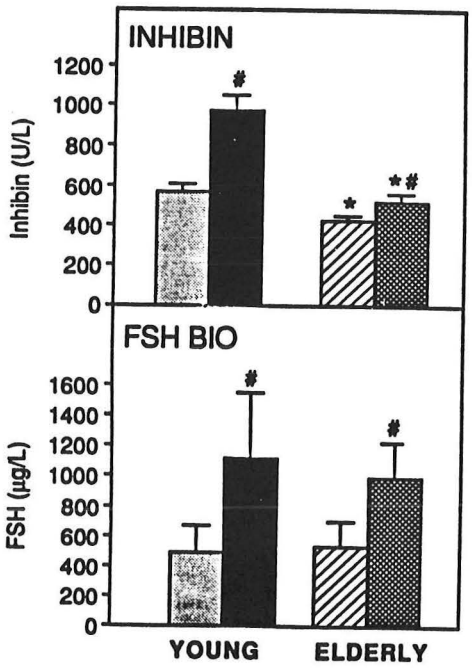


DSP by both testes of 30 men in relation to age. The correlation coefficient and equation of the regression line are shown.

Figure 6

A number of reports have documented histological changes in the seminiferous tubules with age (15-19). These changes include a decrease in tubular volume and tubular length, maturation arrest, multinucleate spermatids, and alterations in Sertoli cell cytoplasm. This pattern of tubular involution is similar to that reported after experimental ischemia (19).

As mentioned above, inhibin is a hormonal product of the seminiferous tubule. There are two reports of decreased serum inhibin levels in elderly men (20, 21). In the first 19 young and 19 elderly men were compared basally and most of them also studied following stimulation of FSH secretion by clomiphene citrate administration. Basal inhibin was lower in the elderly men and increased by only 24% after clomiphene citrate compared to the 71% increase in young men in spite of similar increases in FSH (Fig. 7) (20). The second report studied a larger group (280 men) age 19 to 60 confirming a fall in inhibin with age associated with reciprocal increase in FSH (21).



Mean (±SE) serum inhibin and bioactive FSH levels in 11 young and 13 elderly men before (□ and ▨) and after (■ and ■) 1 week of CC administration. ★, $P < 0.01$ compared to young; #, $P < 0.01$ compared to baseline.

Figure 7

12. Johnson L. A reevaluation of daily sperm output of men. Fertil Steril 37:811-816, 1982

13. Johnson L, Petty CS, Neaves WB. A new approach to quantification of spermatogenesis and its application to germinal cell attrition during human spermiogenesis. Biol Reprod 25:217-226, 1981

14. Neaves WH, Johnson L, Petty CS. Seminiferous tubules and daily sperm production in older adult men with varied numbers of Leydig cells. Biol Reprod 36:301-308, 1987

15. Paniagua R, Amat P, Nistal M, Martin A. Ultrastructural changes in Sertoli cells in aging humans. In J Androl 8:295-312, 1985

16. Nistal M, Codesal J, Paniagua R. Multinucleate spermatids in aging human testes. Arch Androl 16:125-129, 1986

17. Johnson L, Petty CS, Neaves WB. Age-related variation in seminiferous tubules in men. A stereologic evaluation. J Androl 7:316-322, 1986

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19. Paniagua R, Nistal M, Amat P, Rodrigues MC, Martin A. Seminiferous tubule involution in elderly men. Biol Reprod 36:939-947, 1987

20. Tenover JS, McLachlan RI, Dahl KD, Burger HG, DeKretser, Bremner WJ. Decreased serum inhibin levels in normal elderly men: Evidence for a decline in Sertoli cell function with aging. J Clin Endocrinol Metab 67:455-459, 1988

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C. Hypothalamic-Pituitary Function

A normal response of the hypothalamic-pituitary system to decreased testosterone levels and decreased sperm production would be increased LH and FSH secretion. Most studies have reported increased LH levels in elderly healthy men whether normal or decreased serum testosterone levels were observed (3, 22-24 and see Ref. 2 for other references) All investigators report an increased FSH with age (5,9,22). More recent studies have examined not only immunoreactive gonadotropin but also bioactive LH and FSH as assessed in in vitro assays of hormone action. Moreover, the characteristics of secretion of gonadotropins have been assessed by the response to LHRH injection and computer analysis of patterns of serum gonadotropins measured in frequent (often every 10 minute) samples.

The response of LH and FSH to LHRH injection has been observed to be minimally decreased and somewhat delayed in elderly men (22,23). When the sensitivity of the pituitary gonadotrophs to LHRH was assessed by administering small doses of LHRH from 0.625 to 5 µg (compared with the 100 µg usual dose),

elderly men were not found to be less sensitive to LHRH (24). This suggested that any changes demonstrated in LH pulsatile secretion are likely to be a result of alterations in LHRH release. The absence of an increase in serum LH levels sufficient to increase serum testosterone levels to those of young men as well as delayed response to LHRH suggest changes in the hypothalamic-pituitary system in elderly men. One mechanism to account for a subtle defect in the LHRH-gonadotropin axis could be an alteration in feedback sensitivity. Winters et al infused androgens into young and elderly men and found the gonadotropin-suppressive activity of androgen to be increased in elderly men (25). Other investigators using percutaneous androgen for a longer interval also found increased sensitivity of basal serum LH to feedback inhibition in elderly men (26).

There is not a consensus on the nature of the changes in LH pulse frequency and amplitude in elderly men. The group studying young and elderly monks noted a decreased in LH pulse frequency with advancing age but normal pulse amplitude (26). Tenover et al reported that young men have a night-time slowing of pulsatile LH secretion not found in elderly men (27). In the previously cited report of bioavailable testosterone, the mean 24-h immunoactive and bioactive LH were found to be increased in elderly men compared to young men by a similar degree so that the LH bio/immuno ratio was unchanged (8). Moreover, the absolute values of LH in the two assays were similar in both groups of men following clomiphene citrate, and there was no difference in baseline or post-clomiphene LH pulse frequency or mean pulse amplitude. These authors thus concluded that hypothalamic pituitary responsiveness was preserved in elderly men (8). A similar approach was taken by these same investigators in regard to assessment of immunoactive and bioactive FSH (28). Basal bioactive FSH was similar in young and elderly men with a higher immunoactive FSH in the elderly. Administration of clomiphene citrate to young and elderly men increased both bioactive and immunoactive serum FSH with resultant similar levels in both assays. One might argue that basal bioactive FSH should be increased in light of the decreased spermatogenesis and inhibin levels, and thus the hypothalamic-pituitary response basally is not normal.

Dr. Veldhuis and colleagues have championed the importance of computer-assisted deconvolution analysis techniques for inferring from serum concentration profiles the frequency, amplitude, duration, and mass of in vivo hormone secretory bursts as well as the half-life of endogenously released hormone (29). This group initially reported no change with age in immunoactive and bioactive LH as well as the bio/immuno ratio and LH pulse characteristics in the basal state (30). However, pituitary bioactive LH reserve was found to be decreased in older men following LHRH injection or treatment with the antiestrogen tamoxifen. Note that this contrasts with the reported response to a different antiestrogen, clomiphene, by Bremner's group (see above). Recently Veldhuis and colleagues have used this deconvolution analysis to try to imply that a decreased LH secreting burst amplitude might be the basis of the hypoandrogenism in healthy elderly men (31)! I tend to agree with the accompanying editorial concerning this paper (32) that such conclusions are unwarranted. These recent studies used only immunoactive LH when it is known that peak amplitude of bio-LH is significantly different with a different half life. It would seem just as plausible that decreased testosterone levels in these elderly men might trigger increased LH pulse frequency with accompanying lower pulse amplitude.

In summary, there is evidence for increased gonadotropin levels in elderly men. Whether the degree of gonadotropin elevation is appropriate and whether there are alterations in pulsatile secretion is debated.

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28. Tenover JS, Dahl KD, Hsueh AJW, Lim P, Matsumoto AM, Bremner WJ. Serum bioactive and immunoreactive follicle-stimulating hormone levels and the response to clomiphene in healthy young and elderly men. J Clin Endocrinol Metab 64:1103-1107, 1987

29. Veldhuis JD, Carlson ML, Johnson ML. The pituitary gland secretes in bursts: Appraising the nature of glandular secretory impulses by simultaneous multiple-parameter deconvolution of plasma hormone concentrations. Proc Natl Acad Sci USA, 84:7688-7690, 1987

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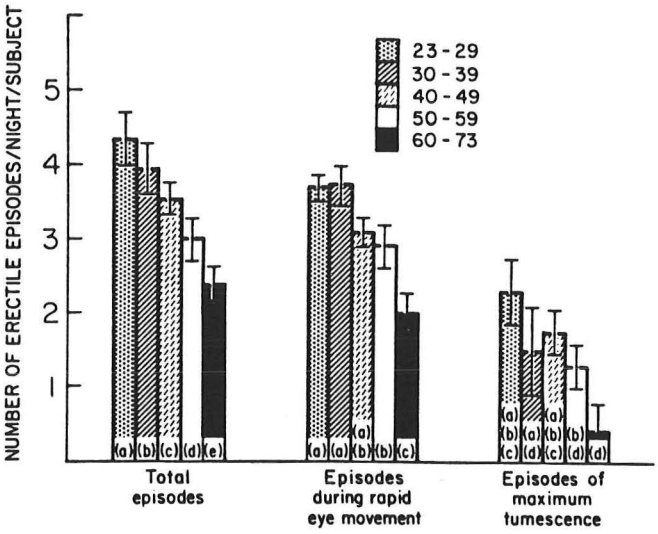
32. Vermeulen A, Kaufman JM. Editorial: Role of the hypothalamo-pituitary function in the hypoandrogenism of healthy aging. J Clin Endocrinol Metab 75:704-706, 1992

II. Does Male Sexual Function Decrease With Age?

There is no doubt that male sexual function declines with age. As most men can confirm from personal experience the rigidity of penile erection and force of expulsion of the ejaculate are greatest and the refractory period is shortest in the late teenage years. Some objective evidence for the early peaking of erectile function can be found in studies of nocturnal penile tumescence in healthy potent men (33,34). Frequency (Fig. 8) and duration of nocturnal penile tumescence, but not degree of circumferential increases during tumescent episodes, decreased progressively with age independent of variations in sleep (33). In contrast to men in younger age groups, the majority of men above age 60 did not have full sleep erections even though they and their partners reported regular intercourse.



Frequency of nocturnal penile tumescent episodes in 5 different age groups. Bars equal mean ± *SEM* of 3 nights per subject. Letters within parentheses at the bottom of bar graphs refer to age groups significantly different from each other ($p < .05$.)

Figure 8

When detailed assessment of healthy aging and male sexual function were made in 65 couples, increasing age was positively correlated with prevalence of reported erectile difficulty and retarded ejaculation but was not associated with problems of sexual desire (34). Although age was significantly related to a decrease in several functional dimensions of male sexuality, sexual enjoyment and satisfaction did not show a decline with increasing age. Nocturnal penile tumescence measures correlated positively with sexual arousal and with frequency of intercourse. Reported erectile problems, but not desire or ejaculatory difficulties, were negatively related to nocturnal penile tumescence variables. Most correlations between behavior and nocturnal penile tumescence lost their significance after age was controlled for. There were no statistical differences in nocturnal penile tumescence measures between the 12 men who reported difficulty in achieving insertion in 50% or more of coital attempts and an age-matched group of 12 nondysfunctional men in the same study.

There are many reports concluding that major sexual dysfunction, when present in elderly men, is more commonly associated with illness rather than aging itself (35-37). Adverse effects of prescribed medications are a common cause of sexual dysfunction in the elderly because of the increased use of medications in this population (38). The major therapeutic categories implicated in drug-induced geriatric sexual dysfunction are the psychotherapeutic agents, such as the antidepressants and neuroleptics and the cardiovascular agents, predominantly the antihypertensives (Table II) (38).

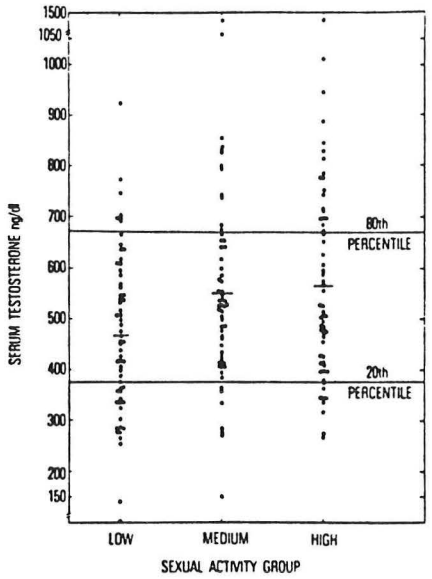
Table II *Drug-Induced Sexual Dysfunction in the Elderly*

DRUG	SEXUAL DYSFUNCTION		
	Libido	*Arousal and Erection*	*Orgasm and Ejaculation*
Psychotherapeutic agents			
Antidepressants			
Heterocyclic	•	•	•
MAOIs	•	•	•
Lithium	•	•	•
Neuroleptics	•	•	•
Anxiolytics	•		•
Cardiovascular agents			
Antihypertensives			
Diuretics/thiazide	?	•	
Spironolactone	•	•	
Methyldopa	•	•	•
Clonidine/guanbenz/ guanfacine	•	•	?
Reserpine	•	•	•
Guanethidine/guanedrel	•	•	•
β-Blockers	•	•	
Hydralazine		•	
Calcium channel blockers			
ACE Inhibitors			
Other cardiovascular agents			
Digoxin	•	•	
Disopyramide		•	
Clofibrate	•	•	
Other drugs			
Cimetidine	•	•	
Metoclopramide	•	•	
Anticonvulsants	•		
Acetazolamide	•		
Chemotherapeutic agents	•	•	
Opioids and narcotics	•	•	•
Alcohol	•	•	•
Nicotine		•	

Table II

Is there any relation of serum testosterone to sexual function in elderly men? In one study of 60-79 year-old, married, upper-middle-class men, frequency of sexual activity appeared to be independent of such factors as marital adjustment, sexual attractiveness of wives, sexual attitudes, and demographic features of the marital history. Former levels of sexual functioning, as revealed by retrospective inquiry, appeared to correlate well with current function (39). These observations were thought to support the hypothesis that men generally maintain relatively high or low rates of sexual activity

throughout their lives. Morning serum testosterone in men categorized as having low, medium, or high levels of sexual activity are shown in Fig. 9 (40). The mean level was found to be significantly lower in the least active group compared to the other two. However, inspection of the individual data would lead one to conclude that serum testosterone alone could not be the sole determinant of such variation in frequency of sexual activity.



Serum testosterone of individuals in each age-adjusted sexual activity group. Horizontal lines in each group indicate the means.

Figure 9

Since bioavailable testosterone declines more than total testosterone in elderly men, studies of bioavailable testosterone might have greater sensitivity for detecting an association with altered sexual function in these men. The group reporting changes in nocturnal penile tumescence with age has also evaluated pituitary-gonadal function in relation to sexual behavior in healthy aging men (41). Sexual desire and reported sleep erections were related to bioavailable testosterone. In contrast, frequency of intercourse, which is presumably influenced by partners' own receptivity, did not show significant hormonal associations. These results are in keeping with evidence primarily derived from hormonal replacement studies in hypogonadal patients that androgens are more important to sustain sexual desire and sleep-releated erections than they are to maintain erectile responses to external stimuli. When the bioavailable testosterone levels were adjusted for the effect of age, the subjects with greater behavioral and sleep erection ratings no longer had significantly higher bioavailable testosterone levels than the less active group (41). The authors concluded that there was no evidence that changes in circulating hormones contribute to erectile disorders in healthy aging men.

Korenman and colleagues have examined the relationship of bioavailable testosterone to sexual dysfunction in older men by looking at the frequency of

low bioavailable testosterone in healthy elderly men claiming normal potency and otherwise healthy elderly men with impotence (Table III) (42). The men with impotence were ones without known endocrine disease, excessive alcohol intakes, or severe debilitating illness. Impotence was defined as inability to complete coitus with vaginal penetration on at least 50% of attempts. The healthy men were recruited at a health fair and had no medical illnesses or medication use. A low bioavailable testosterone was defined as less than 2.5 SD below the mean of a young men control group (mean age 30.3 yr). The percentage of men with low bioavailable testosterone was similar.

Table III. Frequency of Low Bioavailable Testosterone in Healthy Edlerly Men Claiming Normal Potency and Otherwise Healthy Elderly Men with Impotence

	Age (yr)	Men with Bioavailable testosterone < 2.3 nmol/L*
Healthy Potent (n=50)	64.8	48%
Sexual Dysfunction (n=34)	63.8	39%

From Ref. 42
*2.5 SD below mean of young men controls

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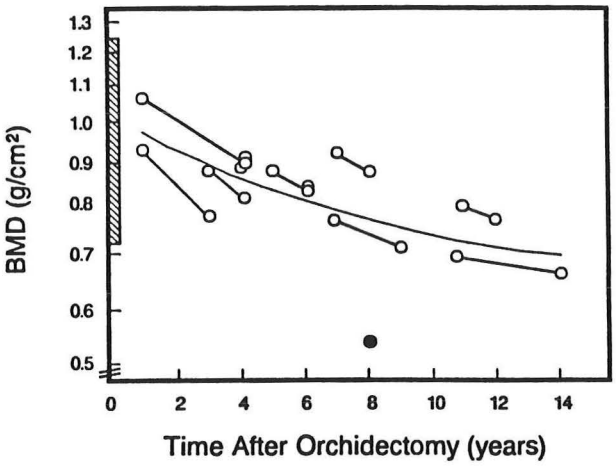
III. Is Hypogonadism or Aging in Men Associated with Decreased Bone Mass?

There is no question that male hypogonadism is associated with a decrease in bone mass. Perhaps the most straight-forward demonstration of the effects of testosterone deficiency on bone density are studies of castration of male sex offenders in pre-democratic Czeckoslovakia (43). Bone mineral density in these men was much less than age-matched normal men, and the longer the time after castration, the lower the bone mineral density (Fig. 10). (43).



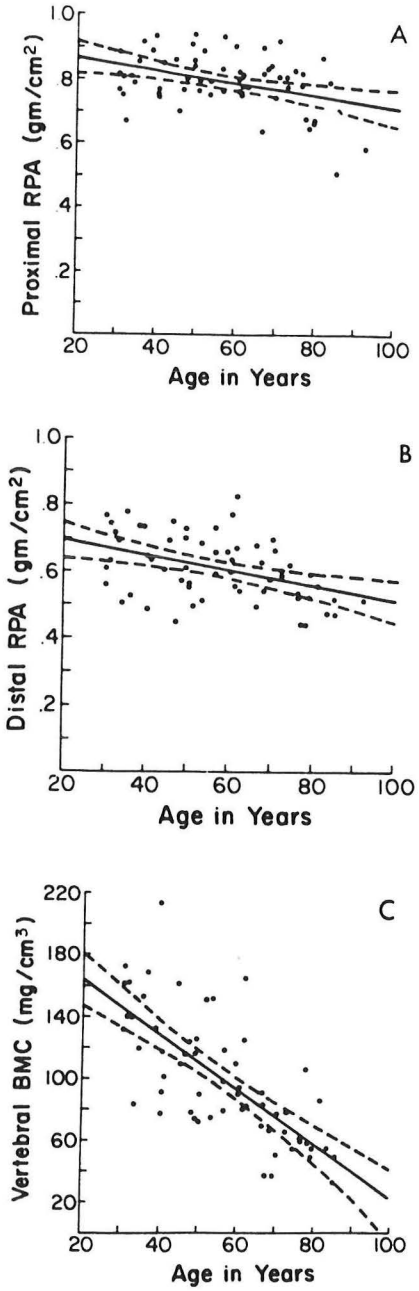
Scattergram of lumbar spinal BMD as a function of time after orchidectomy in 12 men. In 8 patients the measurement was repeated after 1–3 yr (——). The line is regression (second order). Deletion of the repeated measurements made no significant difference to the regression. The *hatched bar* indicates the normal range for 20 men matched for age and is similar to the normal range in men 25–45 yr of age for this laboratory. ●, A value in a man who developed a hip fracture and died from its complications.

Figure 10

Male hypogonadism developing spontaneously has also been associated with decreased bone density including men without normal sexual maturation (e.g. isolated gonadotropin deficiency and Klinefelter's syndrome) (44,45) as well as men who have acquired hypogonadism secondary to pituitary tumors (46,47). Perhaps the most relevant reports are those of men with acquired hypogonadism since studies of men who did not achieve initial sexual maturation have the combined effect of failing to reach an initial normal bone mass. The study of men with hyperprolactinemia is perhaps the most convincing since men were studied before and after receiving treatment for prolactinoma (46). Pretreatment radial and vertebral bone mineral density was significantly lower for the group compared with controls. The group that became eugonadal on therapy had a significant increase in radial bone mineral density and a trend toward increasing vertebral bone mineral density.

In normal men there is progressive decline in bone mineral content with age (48,49). Interestingly there is a marked disparity between trabecular and cortical bone loss with age (Fig 11) (48). Radial bone mineral content (largely cortical bone) fell gradually with age varying from 2.0% per decade for the

proximal radius to 3.4% per decade for distal radius. In contrast, vertebral trabecular content fell more rapidly at 12.2% per decade.



Regression of bone mineral content with age in healthy men (with 95% confidence interval of the estimates) for A) proximal radius, B) distal radius, C) T_{12}-L_3 vertebrae. RPA = radial photon absorptiometry. BMC = bone mineral content.

Figure 11

This 12.2% per decade fall is similar to the 1.2% per year fall in free testosterone in the large population of men described above (Fig. 5). Attempts to relate free testosterone to CT-assessed vertebral bone mineral content in men of increasing age results in a significant association (49). By multiple regression analysis, however, free testosterone levels did not add to the effect of age on vertebral bone mineral content (49).

Looking at a possible relationship of decreased testosterone levels in elderly men and decreased bone density, a case control retrospective study of men in one VA nursing Home Care Unit found that men with a history of prior minimal trauma hip fracture had a greater likelihood of having a free testosterone level below the lower range of young men than otherwise similar men without this history of fracture (Table IV) (50).

Table IV. Comparison of Elderly Men with a History of Minimal Trauma Hip Fracture (MTHF) and Controls in a Nursing Home

	MTHF (n=19)	Control (n=65)
Mean age (yr)	79.6 ± 8.4	76.3 ± 8.6
Free testosterone (pg/ml)	1.4-24.9	1.5-22.8
Mean free testosterone	9.7+ 6.4	12.7+ 4.7
Free testosterone < 9 pg/ml	10/17 (58.8%)*	11/61 (18.0%)
Alcohol abuse	3 (15.8%)	22 (33.8%)
Cigarette abuse	11 (57.9%)	34 (52.3%)
At least one$^{\Delta}$	4 (21.1%)	24 (36.9%)

From Ref. 50
*$p < 0.01$ by logistic regression
Δ At least one of the following present: gastrectomy, nephrolithiasis, cancer, rheumatoid arthritis, thyroid disease, ESRD, or uses of anticonvulsants or glucocorticoids

By odds ratio, white men in this group of nursing home patients with a free testosterone < 9.0 pg/ml were 4.6 times more likely to have a MTHF (95% CI 1.3-16.2). Although this study is limited in interpretation of any causal relationship by its retrospective case control design, it is provocative. Another case control study with a somewhat different means of selecting controls came to a similar conclusion (51). In neither study was bone density assessed.

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IV. What Effect Does Hypogonadism or Aging in Men Have on Lipoproteins?

In spontaneously occurring acquired hypogonadism in men, testosterone deficiency has been associated with increases in total and LDL cholesterol and triglycerides in one study (Table V) (52). The hypogonadal men were divided into those who were hyperprolactinemic and normoprolactinemic. The serum lipid levels in the two groups of hypogonadal men did not differ, nor did the HDL cholesterol of the three groups. The differences noted for the hypogonadal men could not be accounted for by age, body mass index, or age and body mass index together.

Table V. Fasting Serum Lipids and Testosterone Levels in Hypogonadal and Control Men

	Hypogonadal		
	Hyperprolactenemic (n=18)	Normoprolactinemic (n=15)	Control (n=33)
Total cholesterol, mg/dl	241 ± 11*	243 ± 13*	200 ± 11
LDL cholesterol, mg/dl	150 ± 9Δ	168 ± 13*	129 ± 5
HDL cholesterol, mg/dl	47.9 ± 3.8	44.8 ± 3.8	51.8 ± 1.9
Triglycerides, mg/dl	164 ± 23*	143 ± 16Δ	98 ± 6
Testosterone, ng/ml	2.0 ± 0.2*	1.7 ± 0.2*	4.5 ± 0.2

From Ref. 52, * $p < 0.01$ compared to control
Δ $p < 0.05$ compared to control

In experimentally induced hypogonadism resulting from LHRH analog administration, the primary change detected has been an increase in total and HDL cholesterol without a significant change in LDL cholesterol or triglycerides

(53, 54). These changes in lipids were prevented by simultaneous administration of replacement doses of testosterone (53, 54). In the second study in which HDL fractions were measured, HDL_2 increased by 63% and HDL_3 by 17%.

The effects of age on lipoprotein levels can be seen from the data of the Second National Health and Nutrition Examination Survey, 1976-80 (NHANES II) (55, 56). The data from this large population based study are shown for men (Table VI) (55, 56). The pattern is that of a leveling off of the increase in total and LDL cholesterol after age 50 and no change in HDL cholesterol with age in adults.

Table VI. Serum Total, LDL, and HDL Cholesterol Levels in NHANES II for Men

Age group (yrs)	Mean in mg/dl		
	Total	LDL	HDL*
20-24	180	109	45.9
25-34	199	128	44.4
35-44	217	145	43.4
45-54	227	150	43.3
55-64	229	148	44.4
65-74	221	149	44.8

From Refs. 55 and 56, * White men only

It is generally accepted that HDL cholesterol levels decrease about 20% in boys at the time of sexual maturation (reviewed in Ref. 56). However, when attempts are made to correlate total and/or free testosterone levels in adult men with HDL levels, most studies report a positive correlation (reviewed in Ref. 56) while others find no correlation (Ref. 58, and reviewed in Ref. 57). No correlation is found for testosterone and LDL cholesterol in such studies.

In summary, testosterone deficiency might have a negative impact on cardiac risk in regard to LDL levels in studies of spontaneously occurring hypogonadism. A relation of testosterone to LDL in experimental hypogonadism and cross-sectional studies of testosterone levels has not been seen. HDL has a positive correlation with testosterone in many cross-sectional studies but experimental hypogonadism raises HDL in otherwise normal men.

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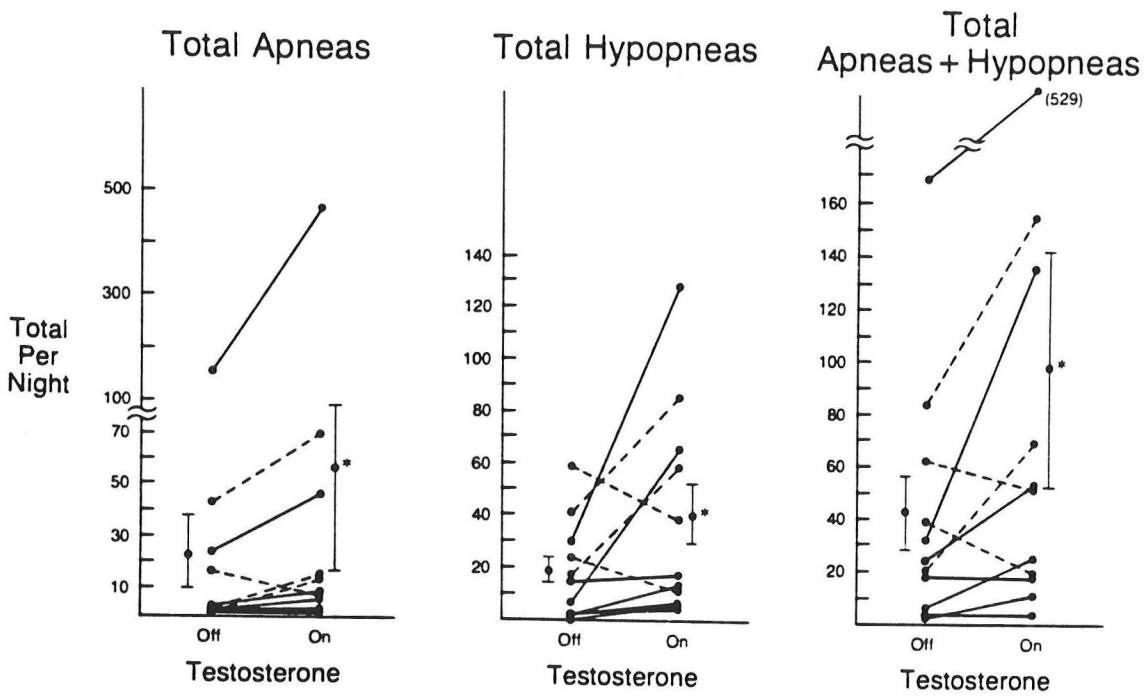
V. Are There Risks or Benefits of Androgen Replacement Therapy in Elderly Men with Low Testosterone?

In young healthy men administration of testosterone in the usual form for androgen replacement, i.e., testosterone cypionate or testosterone enanthate injections, is not associated with adverse effects even when given at three times replacement doses (59). However, in elderly men with clear hypogonadism from a known cause or otherwise healthy with the decreased testosterone typical of the elderly there are several potential risks. The risks arise because testosterone exacerbates several diseases which are particularly prevalent in the elderly: benign prostatic hyperplasia (BPH), prostate cancer, sleep apnea, and polycthemia.

The importance of normal androgen production for BPH is well known (60). Hypogonadal men do not develop BPH. Prostate cancer, with an incidence of 100,000 per year in the U.S. is the most common malignancy of men in this country. Castration or other forms of androgen ablation are known to improve the clinical course of prostate cancer (61). Although exogenous testosterone is probably no more likely to exacerbate BPH or prostate cancer than endogenous testosterone, it seems at least theoretically possible that raising testosterone concentrations to those of younger men might exacerbate testosterone-dependent diseases. However, this has not been specifically shown for BPH and prostate cancer.

Sleep apnea can be defined as greater than 10 apneic episodes (i.e., cessation of breathing for greater than 10 sec) or hypopneic episodes (cessation of breathing for less than 10 sec but accompanied a greater than 4% fall in oxyhemoglobin concentration) per hour during sleep. Increasing age and male sex appear to predispose to sleep apnea (62). When nocturnal sleep studies were performed in hypogonadal men not known to have pulmonary disease, the number of apneic and hypopneic episodes were increased when they were being treated with testosterone compared with when they were not (Fig. 12) (63).



Total number of apneas, hypopneas, and apneas plus hypopneas per night on and off testosterone replacement are demonstrated. Means ± SE are also depicted. There was a significant increase in all 3 events during testosterone replacement. *Solid lines*, subject studied in Denver, CO; *dotted lines*, subject studied in Hershey, PA. *$P < 0.05$, On different from Off testosterone.

Figure 12

The response to androgen was variable with some subjects having a marked increase and others little change. Upper airway dimensions were unaffected by testosterone. Thus, testosterone appears to contribute to sleep-disordered breathing through mechanisms independent of anatomic changes in the upper airway.

Testosterone may also worsen polycythemia. Testosterone is known to stimulate erythropoiesis and is why men have greater hemoglobin concentrations than women. If an elderly man has a propensity for polycythemia due to chronic obstructive pulmonary disease with hypoxia, but is protected somewhat by having a low testosterone, androgen replacement might unmask the polycythemia.

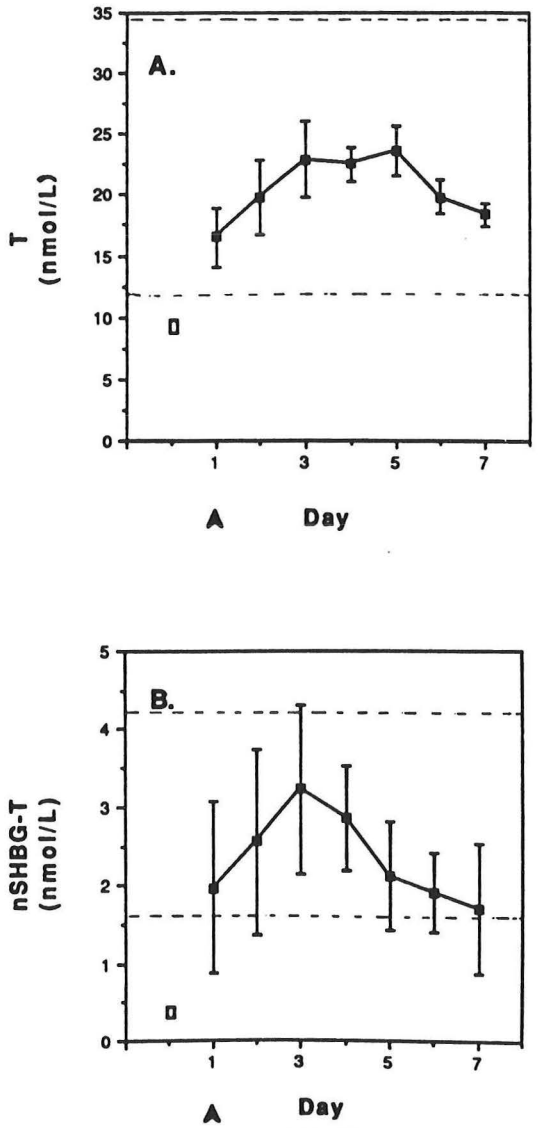
There are certainly benefits of androgen replacement therapy in hypogonadal men, even if they are elderly. Restoration of libido, sexual function, male muscle mass, and energy level are known results of treating male hypogonadism. As described above bone mass may be increased after correction of male hypogonadism. There seems little doubt that the risks described above would not be viewed as so great as to not treat recognized male hypogonadism. However, are there potential benefits of giving testosterone to otherwise healthy elderly men with the reduced levels of bioavailable testosterone seen in a sizable fraction of the population?

There are two recent reports examining this very question. The first is a double-blind placebo-controlled crossover trial in 13 healthy elderly men, all

of whom had serum bioavailable testosterone below the level found in healthy young men (64). In this group the effects of testosterone enanthate 100 mg IM weekly for three months or a vehicle control was assessed on sex steroid levels, gonadotropins, lean body mass, percent body fat, and biochemical parameters of bone turnover. Potential adverse effects of androgen were evaluated by digital prostate exam, prostate ultrasound, voiding urograms, serum prostate-specific antigen (PSA), and serum lipoprotein and hematological profiles.

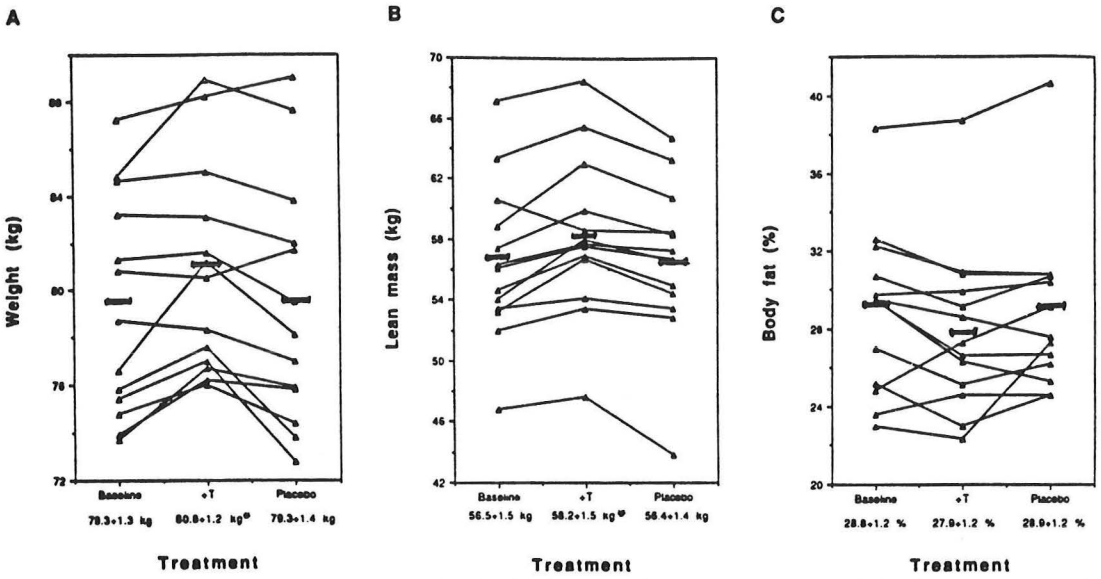
The pattern of serum total and bioavailable testosterone in the fourth week of injections in men in the pilot study are shown in Fig. 13 (64). Values remained in the range for normal young men and considerably above pretreatment levels (open boxes).

Figure 13



. Mean (±SE) morning (0800–1000 h) serum total T (A) and nSHBG-T (B) levels during the fourth week of im TE injections (100 mg/week) in five healthy men, aged 66–76 yr. The *open box* at day 0 represents mean baseline value for that hormone in the five men before any TE treatment. The *arrow* represents the day of injection; serum for that day was drawn just before the injection. The *dotted lines* outline the normal serum range values for the hormone in healthy young adult men.

Likewise, serum dihydrotestosterone and estradiol were normal for young men on therapy. The gonadotropins declined to near-undetectable levels, and SHBG levels decreased. The body composition changes are shown in Fig. 14. Testosterone supplementation resulted in an increase in total body weight and lean body mass without a significant change in percent body fat. These changes were not seen with placebo.



Body weight (A), lean body mass (B), and body fat (C) during baseline, T treatment (+T), and placebo treatment periods in 13 healthy elderly men. The *horizontal lines within each figure* and *numbers below each figure* represent the group mean values. *, $P < 0.01$, by ANOVA.

Figure 14

The only parameter of bone turnover to change was urinary hydroxyproline to creatinine ratio which decreased. This could have been secondary to a rise in urinary creatinine or due to changes in skin since osteocalcin and PTH did not change. The only parameter of prostate function to change was an increase in PSA from 2.1 $\pm$ 0.4 to 2.7 $\pm$ 0.5 ng/ml, $p< 0.01$. It had still not returned to baseline three months after testosterone treatment was discontinued. No abnormalities of routine laboratory parameters were noted, and no men developed acne, gynecomastia or a decrease in testicular size.

The lipoprotein and hematological parameters are shown in Table VII.

Table VII. The Effect of Testosterone Supplementation on Lipoproteins and Hematological Parameters in Healthy Elderly Men

Parameter	Baseline	+Testosterone	Placebo
Total cholesterol (mg/dl)	199 ± 6	177 ± 5*	203 ± 6
LDL cholesterol (mg/dl)	128 ± 7	113 ± 5*	132 ± 7
HDL cholesterol (mg/dl)	49 ± 3	44 ± 2	46 ± 7
Hemoglobin (g/dl)	14.7 ± 0.3	15.5 ± 0.5Δ	144 ± 0.2
Hematocrit (%)	43.1 ± 0.8	46.7 ± 11Δ	43.2 ± 0.8

From Ref. 64. mean + SE
*$p < 0.05$, Δ $p < 0.001$

Testosterone supplementation resulted in significant decreases in total and LDL cholesterol. Triglyceride levels (not shown) did not change significantly. In addition to a significant mean increase in hemoglobin and hematocrit, two men raised their hematocrits to greater than the upper limit of normal (to 51.0% and 54.0%). [Men in the study had been screened to not have preexisting polycythemia].

There is one other study of supplemental testosterone in healthy elderly men using transdermal testosterone reported thus far only in preliminary form (65). Only bone and mineral metabolism parameters were evaluated, but a larger number of men (60 subjects) and a more extensive evaluation of bone parameters was undertaken. Unfortunately no effects of testosterone supplementation were detected (65).

In summary, there are significant risks to treating elderly men with testosterone. Although the benefits of testosterone therapy in defined male hypogonadism are clear, it will require more extensive long term studies of otherwise healthy men with the partial lowering of testosterone typical of aging to confirm whether the benefits of testosterone supplementation are significant.

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