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# Review Article

# ANDROPAUSE: A MISNOMER FOR A TRUE CLINICAL ENTITY

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ABSTRACT

Purpose: A progressive decrease in androgen production is common in males after middle age. The resulting clinical picture has been erroneously named male menopause or andropause. A more appropriate designation is androgen decline in the aging male (ADAM). The syndrome is characterized by alterations in the physical and intellectual domains that correlate with and can be corrected by manipulation of the androgen milieu. We review the epidemiological aspects of aging and endocrinological manifestations of ADAM, and provide recommendations for treatment and monitoring of these patients.

Materials and Methods: We performed MEDLINE, Pubmed, Current Contents and Pharmaceutical Abstracts searches of relevant peer reviewed publications on andropause, male climacteric, adult hypogonadism and aging. In addition, conference proceedings were researched to provide a more complete review of the literature. Information was scrutinized and collated, and contributory data were reviewed and summarized.

Results: ADAM is a clinical entity characterized biochemically by a decrease not only in serum androgen, but also in other hormones, such as growth hormone, melatonin and dehydroepiandrosterone. Clinical manifestations include fatigue, depression, decreased libido, erectile dysfunction, and alterations in mood and cognition.

Conclusions: The onset of ADAM is unpredictable and its manifestations are subtle and variable, which has led to a paucity of interest in its diagnosis and treatment. Urological practice commonly includes a large proportion of men older than 50 years. Therefore, it is important for urologists to recognize the manifestations of and be familiar with evaluations necessary to document ADAM as well as its treatment and monitoring.

KEY WORDS: androgens, hypogonadism, men, aging

"Is it not strange that desire should so many years outlive performance?"[1] In men there is a progressive decline in androgen production associated with aging. This phenomenon has been named male climacteric, andropause or, more appropriately, androgen decline in the aging male (ADAM). The term andropause is biologically incorrect and clinically inappropriate but adequately conveys the concept of emotional and physical changes that, although related to aging in general, are associated with significant hormonal alterations. The inappropriateness of the term is based on the fact that in women the reproductive cycle invariably ends with ovarian failure, while in men this process is not universal. It is normally subtle in its clinical manifestations, which has led to a tendency to ignore the syndrome as an unavoidable and untreatable result of aging. For simplicity and directness we use the terms ADAM and andropause to denote the global hormonal alterations associated with aging.

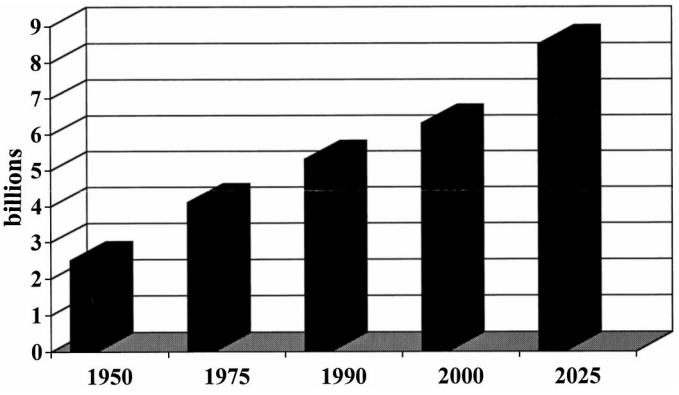


FIG. 1. United Nations projections for world population growth (in billions) within lifetime (75 years).[2]

## EPIDEMIOLOGICAL ASPECTS

The magnitude of the problem has not been clearly defined but population projections indicate that diseases associated specifically with aging will increase significantly in the first half of the next century. Figure 1 shows data from the United Nations estimates and projections of world population trends during a 75-year period.[2] In the last decade of the 20th century the number of humans increased by 1 billion, and it will increase by close to 2 billion during the next 25 years.[3] Perhaps more revealing are the figures for life expectancy, which during the period shown in figure 1 will increase by more than 30 years. In other words, in our lifetimes the number of elderly persons will triple, while the number of children will diminish from 35% to 20% (fig. 2).[4] Therefore, the Earth is hosting a rapidly aging population.

Health problems affecting the elderly today in order of

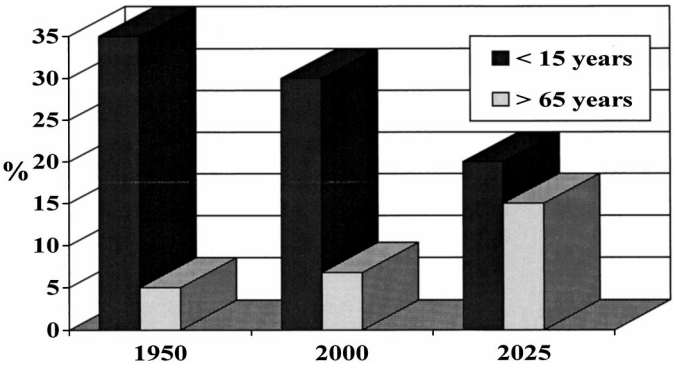


FIG. 2. WHO estimates of nonproductive populations (younger than 15 and older than 65 years) within 75-year span.[4]

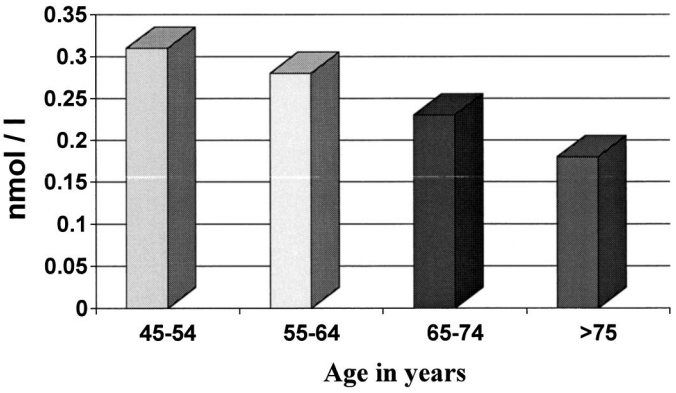


FIG. 4. Decrease in plasma free testosterone relative to age[36]

frequency are cerebrovascular and ischemic heart diseases, cancer, respiratory conditions, Alzheimer's and other dementias, and diabetes. A large proportion of elderly individuals with these diseases will in many ways become part of urological practice. The American Urological Association has identified a number of conditions prevalent in the elderly that will deserve a major commitment for increasing public awareness, such as incontinence, benign prostatic hyperplasia (BPH), prostate cancer and erectile dysfunction.

Age associated alterations in hormone levels in general and androgens in particular in men are significant, and require further research and acceptance by the medical community.[5] Therefore, urologists should view the elderly man who constitutes such a large component of our everyday practice as a patient with more than a specific genitourinary complaint. The nature of such a complaint may be directly related to the hormonal environment. A relevant example is the effects of androgen ablation on men with prostate cancer on bone mineral metabolism[6,7] and sleep patterns.[8] We need to be more aware of the manifestations, proper assessment and treatment of andropause, and the potential complications of hormonal supplementation.

*Hypogonadal states in urological practice.* Urologists easily recognize a variety of hypogonadal states (see Appendix). However, we are less familiar with hypogonadism and other androgen deficiency states associated with age. Our review emphasizes noniatrogenic hypogonadism in middle age and afterwards. A number of central and peripheral endocrinological alterations with aging result in disruption of the regulatory mechanisms of the hypothalamus-pituitary-testicular axis. Figures 3 and 4 show some common alterations in sex hormone profiles with aging.

*Other hormonal alterations associated with advancing age.* It is important to dispel the notion that endocrinopathies of elderly men are narrowly focused on sex hormones. Although hypotestosteronemia is the most widely recognized and evaluated hormonal alteration associated with aging, production of several other hormones is also profoundly affected. Increasing attention is being paid to these hormones because changes can be responsible for some manifestations previously attributed exclusively to testosterone deficiency. The production of growth hormone after puberty also decreases with age by about 14% per decade.[9,10] Since production of circulating insulin-like growth factor-I is controlled by growth hormone levels, both decrease together. This reduction is associated with changes in lean muscle mass, bone density, hair distribution and the pattern of obesity described also in hypogonadal states.[11,12] Administration of growth hormone reverses these alterations[13] and does so more efficiently in eugonadal men than in their hypogonadal counterparts.[14] It is noteworthy that growth hormone determinations are cumbersome and costly.[15] More recently insulin-like growth factor-I has been identified as an anti-apoptotic agent in neuronal model systems.[16] Confirmation of such findings would have major implications, for instance in the prevention of degradation of neurofibril proteins seen in Alzheimer's disease. Although earlier studies supported the concept that administration of growth hormone to adults with growth hormone deficiency improved mood and sense of well-being, such observations have not been supported by more recent controlled studies.[17] A recent review provides detailed information on growth hormone deficiency states.[18]

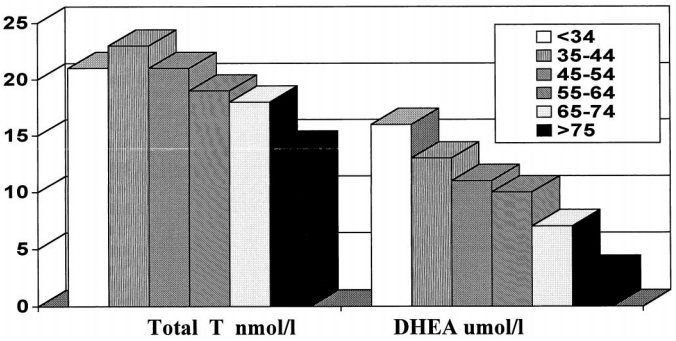


FIG. 3. Mean plasma sex hormones in healthy men reveal alterations associated with aging.[36] Most profound changes occur in serum DHEA. Testosterone (*T*) changes need to be interpreted in conjunction with alterations in SHBG and circadian rhythm.[4]

Melatonin secretion by the pineal gland in response to hypoglycemia and darkness also decreases with age regardless of these stimuli.[19] The physiological role is not completely understood but the pineal gland is involved in gonadal function and regulation of biorhythms.[20] Other physiological effects ranging from analgesic and antioxidative[21] to immunomodulating[22] properties have been attributed to melatonin. Recently evidence was presented indicating that administration of melatonin slows the growth of cancer cells in rodents.[23] However, popular enthusiasm for the hormone has precarious scientific basis. It is likely that administration of melatonin may improve the significant sleep disorders frequently seen in the elderly. As mentioned previously, profound hypotestosteronemia is associated with alterations in melatonin production,[8] therefore making difficult the attribution of some symptoms (sleep disturbances) exclusively to deficits of 1 or the other hormone. Evidence of a wide range of direct and indirect activities of melatonin on many human organ systems is emerging.[24]

In men corticosteroid and estradiol production remains fairly constant throughout life. In contrast leptin, a relatively recently described hormone from adipocytes, is altered in men with hypotestosteronemia which explains in part some of the observed changes in fat distribution.[25] Leptin levels can be decreased by androgen supplementation[26] which usu-

ally results in improvement in obesity.[27] Therefore, it is clear that many of the manifestations associated with the partial sex hormone decline of the aging male can also be attributed to age associated alterations in other endocrine regulatory systems. It follows also that correction of the hypogonadal state may not result in complete resolution of symptoms and single serum hormone determinations may have little correlation with the clinical picture. However, currently there is sufficient evidence to support the concept of an age related process leading to an androgen deficiency state and its associated clinical picture. When response to treatment is considered it is likely that the effects attributed to testosterone supplementation may in fact be mediated by interaction with other hormonal systems.[28]

## ANDROPAUSE

*Clinical manifestations.* In contrast to menopause, the process of andropause is characterized by insidious onset and slow progression. The clinical picture can easily be attributed to natural and unavoidable consequences of aging. True andropause is seen in hormonal ablative treatment of advanced prostate cancer, in which the manifestations are defined more clearly. However, a similar but more subtle picture develops in men affected by ADAM.[29] The andropause syndrome is characterized by 1) the easily recognized features of diminished sexual desire and erectile quality, particularly nocturnal erections; 2) changes in mood with concomitant decreases in intellectual activity, spatial orientation ability, fatigue, depression and anger; [30,31] 3) decrease in lean body mass with associated diminution in muscle volume and strength; [32,33] 4) decrease in body hair and skin alterations; [34] 5) decrease in bone mineral density resulting in osteoporosis,[35] and 6) increase in visceral fat. These manifestations need not all be present to identify the syndrome. In addition, the severity of 1 or more manifestations does not necessarily match that of others, nor do we yet understand their uneven appearance.

*Biochemical changes.* Serum testosterone decreases with age. The onset, speed and depth of the decrease are variable, and to our knowledge no factors have emerged that predict the characteristics or effects of age related hypotestosteronemia. As a rule of thumb, mean serum testosterone decreases approximately 1% per year after age 50 years. However, great interindividual differences exist. Thus, biochemical hypogonadism is detected in only 7% of men younger than 60 years but increases to 20% in those older than 60.[36] Therefore, it may be argued that only a minority of individuals have ADAM, which may not be true. Associated with advancing age is an increase in sex hormone-binding globulin (SHBG) which translates into a further decrease in bioavailable (free and albumin bound fractions) testosterone. An additional phenomenon associated with aging is the flattening of the circadian rhythm leading to steady low levels of androgens throughout the 24-hour cycle.[37] Although not universally accepted, there may also be an androgen deficiency in men with low or borderline serum testosterone in the presence of elevated luteinizing hormone (LH).[38] To compound the difficulties in establishing biochemical and clinical correlates important areas require further elucidation. It is not yet known what level of serum testosterone defines deficiency in an older man, although it is generally accepted that 2 standard deviations below normal values for young men is conclusively abnormal. Also in older men there may be variable responses by the target organs (brain, bone, prostate, muscle and so forth) to androgen levels. The combination of these uncertainties is important as deficiency may become clinically apparent at different times for an individual or a population depending on the marker used.

Urologists are fully aware of extragonadal androgen production because of the widely accepted but still controversial need for total androgen ablation in the treatment of advanced cancer of the prostate. Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are weak androgens secreted primarily by the adrenal glands. They have been touted as cure-alls for the afflictions of aging based on relatively weak documentation. The most appealing arguments are the youthful appearance and behavior of elderly rats treated with DHEA and testimonials of humans on the extraordinary properties of these hormones. To balance the picture it should be remembered that DHEA and DHEAS are evolutionary hormones absent in rodents and present only in higher primates. As for the testimonials the power of the placebo is well recognized.[39] Small, short trials have shown that exogenous DHEA does not have detrimental effect on prostate specific antigen (PSA).[40] However, only properly controlled long-term studies will provide a clear picture of the effectiveness of adrenal androgens in the treatment of global androgen deficiency states. Nevertheless, DHEAS is a neurosteroid synthesized in the brain that promotes neuronal growth and regeneration.[41] An inverse correlation has also been reported between organic brain syndrome and DHEAS.[42] Nevertheless, behavioral correlates of DHEA and DHEAS in males are inconsistent[43] and consensus on their usefulness does not exist.[44]

The decrease in DHEA and DHEAS is a much more constant feature of advancing age than hypogonadism. By the 5th decade of life DHEA levels decrease to less than 30% of those in men younger than 30 years.[45] There is widespread belief that declining levels of DHEA parallel a decrease in well-being, and Morales et al reported that supplemental exogenous DHEA results in improvement in quality of life parameters.[46]

*Biochemical manifestations.* Hormonal evaluation of men with erectile dysfunction has been questioned on the basis that it is not cost-effective.[47] This skepticism is not shared by most investigators.[48,49] There are several reasons to justify at least basic hormonal assessment of men with erectile dysfunction. It is commonly accepted that the combination of low sexual desire and erectile difficulties may be the result of serious hormonal abnormalities. The reality is not that clear-cut. Not only may hypogonadal men be capable of adequate sexual erections, but hormonal supplementation resulting in normal testosterone values does not always result in restoration of libido and quality of erectile function.[50] Furthermore, penile erections have been documented in human male fetuses and castrated subjects. However, most important is the fact that the population seeking advice for erectile dysfunction comprises the majority of the same group in which hormonal alterations associated with aging are commonly found. It behooves the urologist to be aware of and assume a proactive attitude toward the diagnosis of these deficiencies, and to treat or refer them depending on his/her interests and expertise. One must remember that, except for the most profound deficiencies, adult onset hypogonadism is difficult to diagnose on a purely clinical basis. Therefore, it is recommended that biochemical evaluations be performed on patients at risk for or suspected of having hypogonadism. Serum testosterone assessment should be done between 8 and 11 a.m.

The best parameter to determine hypogonadism is measurement of bioavailable testosterone, which includes free and albumin bound fractions. In men older than middle age total testosterone may be misleading due to alterations in SHBG and flattening of the circadian rhythm mentioned previously. If testosterone is below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination with assessment of LH, follicle-stimulating hormone (FSH) and prolactin. In the younger male low testosterone levels (less than 12 nmol./l. or 350 ng./dl.) and chronically elevated gonadotropins make a clear diagnosis of primary hypogonadism or testicular failure. In an older man the diagnostic lines are not as clearly defined

and additional information may be needed. Thus, in these men as well as in the obese SHBG determination may be useful in establishing the true clinical significance of testosterone measurements. Although secondary (hypogonadotropic) hypogonadism is usually also treated with androgen supplementation, more thorough endocrinological assessment is recommended. A correctable cause or a different therapeutic approach may be more appropriate than simple androgen administration. A practical diagnostic algorithm is shown in figure 6.

*Medical treatment.* Goals of medical treatment for androgen deficiency include restoration of sexual functioning as well as libido and sense of well-being. Additionally, androgen replacement can prevent osteoporosis and optimize bone density, maintain virilization, improve mental acuity and restore normal growth hormone levels, especially in elderly males.[30,51] Testosterone replacement therapy should maintain not only physiological levels of serum testosterone, but also the metabolites of testosterone, including dihydrotestosterone and estradiol, to optimize maintenance of libido, virilization and sexual function. Current treatment options include oral tablets and capsules, long and short acting intramuscular preparations, implantable long acting slow release pellets, and scrotal and nonscrotal transdermal patches. Neither injectable preparations nor slow release pellets reproduce the circadian pattern of testosterone production of the testes, which is accomplished best with dermal patches, although oral testosterone may also approximate a circadian rhythm by dose adjustments. Common testosterone preparations are shown in the table.

Oral preparations of testosterone require special consideration. Since most undergo rapid hepatic metabolism they may fail to establish satisfactory serum levels of androgens.[52] Oral agents available in the United States include the alkylated (to prevent rapid hepatic metabolism) androgen preparations which generally provide erratic androgenic effects and significant changes in lipid profile, and have a high risk of adverse liver side effects.[50] Hepatotoxicity includes hepatocellular adenoma, cholestatic jaundice and hemorrhagic liver cysts.[53] In addition, alkylated androgens may result in increased low and decreased high density lipoproteins with resultant possible increased cardiovascular risks.[54] Although not available in the United States, testosterone undecanoate is widely used throughout the world. As a testosterone ester (the only one effective orally), it is free of liver toxicity and effective in bringing serum testosterone within physiological range. However, it may result in supraphysiological levels of dihydrotestosterone and rarely gastrointestinal side effects.[55] The medication is lipid soluble and should be taken with meals. The recommended dose is 120 to 200 mg. in 3 divided doses, depending on the degree of testosterone deficiency, body surface, obesity and clinical response.

*Commonly used testosterone preparations*

| | Trade Name | Mg. Dose (frequency) |
|---|---|---|
| Injectable: | | |
| Testosterone cypionate | Depo-testosterone cypionate | 200–400 (every 3–4 wks.) |
| Testosterone enanthate | Delatestryl* | 200–400 (every 4 wks.) |
| Oral: | | |
| Fluoxymesterone† | Halotestin‡ | 5–20 (daily) |
| Methyltestosterone† | Metandren§ | 10–30 (daily) |
| Testosterone undecanoate | Andriol‖ | 120–240 (daily) |
| Transdermal testosterone patch | Androderm, Testoderm | 6 (daily) |

* Bio-Technology General Corp., Iselin, New Jersey.
† These 17$\alpha$ alkylated testosterone products are associated with serious liver toxicity.
‡ Pharmacia & Upjohn, Kalamazoo, Michigan.
§ Novartis Pharmaceuticals, Basel, Switzerland.
‖ Organon, Oss, The Netherlands.

Most testosterone preparations for intramuscular injection obtain maximum concentration approximately 72 hours after injection which slowly diminishes during the ensuing 10 to 14 days.[56] This gradual decline frequently results in a low nadir before repeat injection.[57] Parenteral androgens do not provide normal circadian patterns of serum testosterone and the injections are somewhat uncomfortable. Levels of dihydrotestosterone are normal but androgen metabolites are frequently not physiological while estradiol may become excessive in some men. Supraphysiological levels of serum testosterone occur following injections, which may result occasionally in breast tenderness or gynecomastia. Intramuscular testosterone may also be administered as unmodified aqueous testosterone in its most elemental form. However, this preparation is rapidly absorbed and degraded, requires frequent administration and is unsatisfactory for chronic testosterone replacement.

More widely used preparations include 17-$\beta$-hydroxyl esters of testosterone which are administered with slow release oil based injection vehicles. However, these esters lack inherent androgenic activity and must be hydrolyzed to testosterone to become pharmacologically active. The 17-$\beta$-hydroxyl esters of testosterone most widely used in the United States include short acting testosterone propionate, and longer acting testosterone enanthate and cypionate. Testosterone propionate is rarely used clinically because of its short half-life and requirement for every other day injection to maintain normal serum testosterone. Testosterone enanthate and cypionate may be administered every 10 to 21 days to maintain normal average testosterone. It must be acknowledged that testosterone surges to supraphysiological levels as high as 1,400 ng./ml. approximately 72 hours after administration of these preparations.[52] The decrease in serum testosterone continues for 14 to 21 days reaching baseline at approximately day 21.

The significant peaks and valleys of serum testosterone in patients treated with parenteral testosterone injections may produce significant mood swings, and noticeable ups and downs in libido and sexual function. However, these long acting testosterone preparations are the most cost-effective methods for testosterone replacement, with administration of 200 to 400 mg. every 2 to 4 weeks. The 200 mg. injections will maintain normal testosterone for approximately 2 weeks while 300 mg. doses are required for eugonadal range for

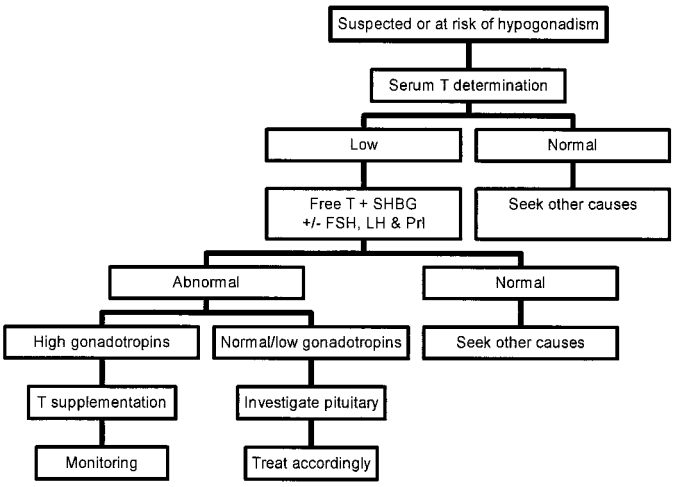


FIG. 5. Practical diagnostic algorithm for biochemical evaluation of men suspected of ADAM. Androgens are not only hormones that decrease with advancing age. *T*, testosterone. *Prl*, prolactin.

approximately 3 weeks.[58] Higher doses will not maintain testosterone levels in the normal range beyond the 3-week limit. These agents have clearly been demonstrated to improve libido, sexual function, potency, energy level, bone density and mood if these abnormalities are caused by androgen deficiency. Supraphysiological levels of serum testosterone may result in infertility due to suppression of FSH and LH production.[59] Reports of sexual aggressiveness and overall aggressive behavior during peak levels following injectable testosterone have been reported anecdotally. Counseling about the possibility of these mood and behavioral changes for patients undergoing parenteral testosterone therapy is essential.

Tan et al recently reported the effects of parenteral testosterone on high density lipoproteins in 11 men receiving 250 mg. testosterone enanthate at 4 weekly intervals.[60] Although these doses resulted in suboptimal serum levels of testosterone, no significant changes in plasma cholesterol, triglycerides, or low or high density lipoproteins occurred. Injectable testosterone has also been implicated in abnormal erythropoiesis and increased hemoglobin, and sometimes hypercoagulability.[61] However, these changes have not been demonstrated with newer transdermal preparations.[62] There are justified concerns about elevated testosterone in elderly men and associated PSA elevations, increased prostatic size with associated obstructive symptoms and the activation of occult prostatic malignancy.[63–65] While some increases in PSA and prostate specific membrane antigen as well as increased prostatic size have been documented, these changes are not statistically significantly different from those in untreated hypogonadal men.[66] Similarly, PSA elevations have not increased above normal clinical values.

Transdermal testosterone therapy, a more expensive but more physiological approach to testosterone replacement, has recently become available worldwide.[67] These preparations, which are available in scrotal and nonscrotal patches, use elemental testosterone absorbed transdermally to obtain normal serum testosterone and reproduce the diurnal physiological variations observed in normal human testosterone secretion. Patches are applied at bedtime with peak testosterone achieved in the early morning and a nadir before patch replacement. The first available patch was scrotal, required weekly scrotal shaving, and was difficult for some patients to apply and maintain in position for 24 hours. Patients with small rugose scrotums had difficulties with absorbing higher doses of testosterone.[68] The scrotal patch, while obtaining normal physiological testosterone and normal estradiol levels, was demonstrated to have abnormally high dihydrotestosterone as a result of high concentrations of 5$\alpha$-reductase in the scrotal skin.[62]

Transdermal patches now available for nonscrotal use include the Androderm* and Testoderm† systems.[69,70] These nonscrotal patches also maintain normal diurnal serum estradiol and dihydrotestosterone. While most patients can be treated with a single nonscrotal transdermal patch, some require more or less testosterone replacement depending on deficiency and absorption characteristics. Morning testosterone should be evaluated within 2 to 3 weeks of initiating therapy to identify peak levels. Serum evaluations should be performed between 8 and 10 a.m. to determine the highest daily level of serum testosterone produced by the patch. Because androgen levels do not increase above normal with these systems, it is unlikely that there will be detrimental changes in mood with transdermal preparations.

Although psychological effects have not been carefully studied in a long-term series, to our knowledge no cases of aggressiveness with the transdermal patch systems have been reported.[71] However, followup studies of transdermal testosterone replacement have demonstrated improvement in testosterone associated with improved sexual function, libido and nocturnal penile tumescence response, with maintenance of normal hematocrit, lipid profile, PSA and prostatic volumes.[69,71,72] Dermal patches may be inconvenient to apply and common side effects include dermatitis, sometimes leading to significant chemical burns.[73,74] To our knowledge comparative studies on patient and physician preferences between scrotal and transdermal patches are not available. Whether scrotal patches are still extensively used is not known, although they have the advantage of less skin irritation but the disadvantage of scrotal application.

Investigational techniques for testosterone replacement include long acting implantable percutaneous pellets,[75] spheres and microcapsules under study in Europe.[76] These subcutaneous capsules are fused pellets of unmodified testosterone implanted every 4 to 6 months. Because these pellets require the use of a trocar or a minor surgical procedure they are less appealing than other testosterone preparations. Further development of these pellets to decrease invasiveness of administration and increase patient acceptance may lead their use as long-term testosterone replacement therapy. The longevity of implants and microcapsules, and difficulty in removal if serious adverse events occur make them less attractive for elderly patients.[77]

*Monitoring patients on hormonal replacement.* Hormonal replacement may be initiated for a variety of indications but treatment is normally for life. Monitoring is also a lifetime commitment that cannot be taken lightly, and requires tailoring to the indications and individual needs of the patient. For instance, for osteoporosis serial bone density determination is the method for monitoring therapeutic response. In this regard Behre et al have illustrated the effectiveness of chronic androgen supplementation in increasing bone mineral density and in moving older men out of the range of high fracture risk.[78] In urology the most common indication for testosterone administration is treatment of erectile dysfunction. Frequently patient reports are the most reliable indicators of treatment effectiveness.[52] In addition to the specific areas of interest, long-term monitoring is based on concern for possible serious adverse events in 5 domains, namely 1) the liver, 2) lipid profile and cardiovascular disease, 3) prostate, 4) sleep disorders, and 5) social behavior and emotional state.

Liver: Reports of liver toxicity manifested by jaundice and alteration of liver function studies as a result of pielosis as well as the development of hepatic carcinoma have been limited almost exclusively to cases treated with methylated forms of testosterone. Injectable, dermal and oral agents without methyltestosterone are safe in this regard. Nevertheless, yearly liver function tests following institution of androgen therapy are advisable.

Lipid Profile and Cardiovascular Disease: The question of alterations in lipid profile in hypogonadal men remains to be fully resolved. However, evidence is emerging that supports the concept of low testosterone levels associated with potentially unfavorable changes in triglycerides and high density lipoprotein cholesterol, and that such abnormalities can be corrected by restoring physiological levels of androgens.[79] On the other hand, some concern exists about elevations in low density lipoprotein cholesterol following administration of exogenous androgens. These changes are modest but clinical consequences have not been clarified.[80] A study by Phillips et al raised the possibility that hypotestosteronemia may be a risk factor for coronary artery disease,[81] which subsequently was supported by Uyanik et al.[82] The relationships between androgens and cardiovascular risk factors are complex and not completely defined.[83] Although much evaluation is being directed to explore these relationships, careful followup is advisable when supplementing androgens in patients with significant risk factors for cardiovascular disease.

Prostate: The most serious concerns with the use of andro-

* SmithKline Beecham, Philadelphia, Pennsylvania.
† Alza Corp., Palo Alto, California.

gen supplementation are expressed in relation to benign and malignant conditions of the prostate. The urologist is frequently consulted in this regard. According to current opinion the development of BPH is mediated by intraprostatic events due to the action of 5$\alpha$-dehydrotestosterone[84] most likely with active participation of estrogenic influences.[85] It has long been recognized that prostate volume increases with age in normal men but not in their untreated hypogonadal counterparts. When hormonally deficient men are treated prostate volume increases but only to the size expected for eugonadal men of the same age.[86] The relationship between lower urinary tract symptoms and their objective correlates to androgens is being redefined. Earlier studies supported the view that androgen administration resulted in a modest but significant increase in prostate volume and PSA which, nevertheless, remain within normal limits.[66,87] Most studies have shown no effect of exogenous androgens on PSA or prostate volume.[33,78] More recent evidence from placebo controlled studies of hypogonadal men receiving androgen therapy indicates that the differences between those receiving testosterone and those on placebo were insignificant in regard to prostate volume, PSA and lower urinary tract symptoms.[88,89]

Much speculation exists regarding serum testosterone and the prostate gland. Only the concept that testosterone promotes growth of an established adenocarcinoma is firmly established. Whether testosterone also promotes the development of prostate cancer remains to be elucidated. The evidence is to the contrary but still insufficient to rule out conclusively a causal risk. Current knowledge indicates that serum sex hormones have no relation to the development of prostate cancer[90] and there is no change or only a modest (within normal range) increase in PSA after testosterone administration. Of the dozen or so studies evaluating prostate changes following androgen administration only a few have reported an increase in PSA.[90–92] Nevertheless, caution is needed. The preponderance of evidence of only marginal or no changes in PSA indicates that androgen supplementation does not result in serious prostatic disorders but only for a few years. This experience is too short to establish the long-term safety of exogenous testosterone administration in regard to prostatic cancer but to our knowledge there is no credible evidence that prostatic biopsies are indicated before initiation of androgen supplementation. However, a rapid increase in PSA or detection of abnormalities by digital rectal examination after androgen supplementation is a clear indication for further evaluation. It follows that normalization of the androgen milieu could provide early clues for the presence of occult carcinoma of the prostate.[93]

Sleep Disorders, and Social Behavior and Emotional State: Sleep apnea may be exacerbated during the administration of exogenous testosterone.[94] Caution is indicated if androgens are prescribed for a patient with previously documented or suspected sleep apnea. The use of antiandrogens and castration has been advocated for rapists and others with sexually aggressive behaviors, which has sustained the belief that androgen supplementation results in enhancement of aggressiveness. This issue remains unresolved.[95] Testosterone administration to eugonadal or hypogonadal men resulting in serum testosterone within normal range does not result in pathological behavior.[96] Testosterone can be implicated in only a small proportion of men with aggressive personalities.[97,98]

## RECOMMENDATIONS

Our understanding of ADAM is still incomplete and there are a number of controversial issues in regard to hormonal replacement in elderly men. Therefore, standards and guidelines on the subject may be premature. However, recommendations are justified with the present state of knowledge, and those recently provided require frequent updates as further information emerges.[99,100]

Men must have a clear indication for administration of exogenous testosterone. No patient is too old to receive testosterone therapy if clearly indicated. Men with suspected secondary hypogonadism of hypothalamic pituitary origin should be thoroughly evaluated before hormonal replacement. Digital rectal examination and serum PSA determination are mandatory before starting androgen replacement therapy. Androgen treatment may be suitable for men with mild lower urinary tract symptoms but not for those with marked symptoms. Known prostate or breast cancer is an absolute contraindication for testosterone treatment. Injectable or oral testosterone esters as well as dermal patches are recommended because of safety. The 17 alkylated oral steroids are to be avoided due to erratic absorption and potential for toxicity. For the first year after onset of therapy patients should be followed quarterly to assess clinical and biochemical response, with digital rectal examination and PSA if they are older than 40 years. Patients who remain stable may subsequently be followed annually, at which time other tests should include hemoglobin, liver function, lipid profile and serum calcium. Bone density, psychological evaluation and so forth should be performed depending on the initial indications for androgen supplementation. Serum testosterone will fluctuate considerably, particularly after intramuscular administration. Clinical response is a better guide to dose requirements, regardless of serum testosterone levels.

## CONCLUSIONS

There is clear evidence that advancing age is associated with a decrease in production of several hormones. The most prominent alterations are related to the sex steroids but others, such as growth hormone and melatonin, are also profoundly affected. The clinical syndrome of ADAM or andropause has been described but a direct causality between its manifestations and alterations of a specific hormone are not yet fully established. The patient population in a urology practice frequently involves individuals older than middle age, when hypoandrogenism becomes most prevalent. It behooves the urologist to be familiar with the consequences, evaluation, treatment and monitoring of this condition.

## APPENDIX: HYPOGONADAL STATES

- Hypothalamic pituitary disorders:
  - Panhypopituitarism
  - Isolated LH deficiency
  - LH and FSH deficiency (Kallmann's syndrome)
  - Biologically inactive LH
- Gonadal abnormalities:
  - Klinefelter's syndrome
  - Other chromosomal defects
  - Bilateral anorchia
  - Leydig cell aplasia
  - Adult Leydig cell failure (ADAM, andropause)
  - Defects in androgen biosynthesis
- Defects in androgen action:
  - Complete insensitivity
  - Incomplete insensitivity type I
  - Incomplete insensitivity type II 5$\alpha$-reductase deficiency

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