A Review of the Chemistry, Biological Action, and Clinical Applications of Anabolic-Androgenic Steroids

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ABSTRACT

Background: Since its discovery in 1935, numerous derivatives of testosterone have been synthesized, with the goals of prolonging its biological activity in vivo, producing orally active androgens, and developing products, commonly referred to as anabolic-androgenic steroids (AAS), that are more anabolic and less androgenic than the parent molecule.

Objective: This article reviews the structure, biotransformation, and mechanism of action of testosterone and some of the most commonly used AAS. Clinical applications of the AAS are discussed, and guidelines and therapeutic maneuvers for minimizing their side effects are outlined.

Methods: Literature for inclusion in this review was identified using the libraries of the University of Wisconsin Medical School and School of Pharmacy, the author’s files, and searches of MEDLINE, Science Citation Index, Biological Abstracts, and Chemical Abstracts.

Results: The myotrophic action of testosterone and its derivatives and their stimulatory effects on the brain have led to widespread use of AAS by athletes and “recreational” drug users. Consequently, all AAS were classified as class III controlled substances in 1991. Nonetheless, AAS have shown benefit in a variety of human disorders, including HIV-related muscle wasting and other catabolic conditions such as chronic obstructive pulmonary disease, severe burn injuries, and alcoholic hepatitis. Because of their diverse biological actions, AAS have been used to treat a variety of other conditions, including bone marrow failure syndromes, constitutional growth retardation in children, and hereditary angioedema. AAS therapy is associated with various side effects that are generally dose related; therefore, illicit use of megadoses of AAS for the purpose of bodybuilding and enhancement of athletic performance can lead to serious and irreversible organ damage. The most common side effects of AAS are some degree of masculinization in women and children, behavioral changes (e.g., aggression), hepatotoxicity, and alteration of blood lipid levels and coagulation factors.

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**Conclusions:** To minimize or avoid serious toxicities with AAS therapy, close medical supervision and periodic monitoring are important, with dose adjustment as appropriate to achieve the minimum effective dose. Given the biological effects and potential adverse effects of AAS, administration of these agents should be avoided in pregnant women, women with breast cancer or hypercalcemia, men with carcinoma of the prostate or breast, and patients with nephrotic syndromes or significant liver dysfunction.

**Key words:** testosterone, anabolic-androgenic steroids, anabolic steroids. *(Clin Ther. 2001;23:1355-1390)*

**INTRODUCTION**

The isolation, synthesis, and characterization of testosterone in 1935 by several independent researchers in Europe led to further study of this hormone and a better understanding of its biological effects. Testosterone has been found to exert its effects—designated as androgenic and anabolic—on both reproductive and non-reproductive target tissues. Androgenic effects are responsible for growth of the male reproductive tract and development of secondary sexual characteristics, whereas anabolic effects stimulate nitrogen fixation and increased protein synthesis. The potential therapeutic value of testosterone’s anabolic activity in various catabolic conditions has led to synthesis of many derivatives, with the goals of prolonging the biological activity of the parent molecule in vivo, producing orally active androgens, and developing products that are less androgenic and more anabolic. Although complete dissociation of testosterone’s androgenic and anabolic effects has not been achieved, some of the anabolic steroids—more appropriately called anabolic-androgenic steroids (AAS)—have shown significant anabolic activity with somewhat reduced androgenicity.

The anabolic activity of testosterone and its derivatives is primarily manifested in its myotrophic action, which results in greater muscle mass and strength. This, in conjunction with the stimulatory effects of androgens on the brain—which frequently result in a feeling of euphoria and increased aggressiveness—has led to widespread use of AAS by athletes at all levels, as well as “recreational” drug users. However, the benefits of AAS in athletes remain controversial. This medically unsupervised use and misuse of megadoses of AAS and the resultant physical and psychological side effects have inspired a large body of literature, whereas comprehensive reviews of the legitimate clinical uses of AAS have been scarce. In 1990, in response to the problem of clandestine manufacture and illegal sale of AAS, the US Congress passed legislation making the AAS class II! controlled substances as of February 1991.

Despite the adverse publicity surrounding the AAS, judicious prescription of these agents by physicians can greatly improve outcomes in a variety of human disorders, including conditions associated with catabolic states, bone marrow failure syndromes, constitutional growth retardation in children, and hereditary angioedema. This article reviews the structure, biotransformation, and mechanism of action of testosterone and some of its most commonly used synthetic derivatives; discusses the clinical applications of AAS; outlines certain guidelines for their use; and suggests therapeutic measures to minimize their side effects. Literature for inclusion in this review was iden-
STRUCTURE AND BIOTRANSFORMATION OF TESTOSTERONE

The main natural androgen testosterone undergoes a series of biotransformations by oxidoreductive reactions at C3, C4, C5, and C17 (Figure 1). The first step in the metabolism of testosterone is reduction of the C4,5 double bond, resulting in formation of 5α and 5β derivatives in which the hydrogens at C5 are respectively above and below the planar molecule, making them different in spatial configuration. Among the metabolites, 17β-hydroxy-5α derivatives such as 5α-dihydrotestosterone (DHT) are androgenic, whereas 5β steroids are not. 5α-DHT is produced by 5α-reductase in target organs such as the brain and reproductive tract, and 5β steroids are formed in the liver by 5β-reductase.

Reduction of the C4,5 double bond is irreversible. The testosterone molecule and some of its synthetic derivatives (eg, C4,5 testosterone esters) with unsaturated C4,5 can be converted to estradiol by aromatase in tissues such as adipocytes and the brain, whereas DHT and other 5α synthetic derivatives cannot be converted. After reduction of the C4,5 double bond, the 3-keto group of the 5α isomer is rapidly reduced by either 3α-hydroxysteroid dehydrogenase or 3β-hydroxysteroid dehydrogenase. After oral administration or IM injection, testosterone is metabolized mainly to 3α-hydroxy isomers, with formation of only small amounts of the 3β-hydroxy-5α metabolite.

Another important metabolic pathway of testosterone is oxidation of the 17β-hydroxy group in the D ring. In this step, which is mediated by 17β-hydroxy dehydrogenase, 17-keto metabolites are formed. However, the 17-keto group can be converted back to the hydroxy group by the same enzyme. 17-Keto derivatives such

![Figure 1. Aspects of testosterone biotransformation.](image-url)
as androsterone and etiocholanolone are the main urinary metabolites of testosterone. Thus, on oral or parenteral administration, the 17β-hydroxy group is rapidly oxidized to biologically inactive polar metabolites.

To overcome the rapid biotransformation of testosterone and synthesize longer-acting and/or orally active compounds with lower androgenicity and higher anabolic activity, more than 100 synthetic steroids have been developed. Among the many modifications that have been made to the testosterone molecule, those described in the following sections have been most effective in achieving the stated goals and form the basis of the AAS most commonly used today.

17α-Alkylation

When the testosterone molecule is modified by 17α-alkylation, a methyl group (CH₃) is commonly introduced at position C17α. Methyltestosterone, synthesized in 1935 by Ruzicka et al. was among the first 17α-alkylated androgens; others in this group include oxymetholone, oxandrolone, and stanozolol. In other 17α-alkylated androgens such as norethandroline, ethylestrenol, and norbolethone, an ethyl group (C₂H₅) is introduced at position C17α.

17α-Alkylation markedly retards hepatic inactivation of testosterone and thus allows these products to become orally active. With the exception of methenolone, which is alkylated in the C1 position, all orally active androgens are 17α-alkylated.

17β-Esterification

Esterification of the 17-hydroxy group with long-chain hydrocarbon molecules delays biodegradation of testosterone to keto steroids. The products in this group are active only on parenteral administration. The type of acid used to acetylate the 17β-hydroxy group determines the duration of anabolic action. Short-chain esters (eg, C₂-C₃) give rise to short-acting steroids, whereas long-chain esters (eg, C₇-C₁₀) are long-acting compounds. Like testosterone itself, these derivatives are highly androgenic and, by virtue of their unsaturated C4,5 double bond, can be aromatized.

Substitution of hydrogen for the methyl group of C19 results in the formation of 19-nortestosterone (nandrolone). This hydrogen substitution has the same β configuration as the methyl group of testosterone. Esterification of the 17-hydroxy group of nandrolone with phenylpropionic acid (nandrolone phenylpropionate) or cyclopentylpropionate (nandrolone cypionate) yields products that are more stable and more anabolic. Esterification of the 17-hydroxy group of nandrolone with decanoic acid, a long-chain fatty acid, yields nandrolone decanoate, which is released into the circulation slowly on deep IM injection and which exerts its optimal anabolic activity over 6 to 7 days. Despite an unsaturated C4,5 double bond, 19-nortestosterone derivatives have significantly less androgenic activity compared with testosterone esters.

Most Commonly Used Testosterone Derivatives

Because the aim of this report is to describe clinical applications of the anabolic activity of AAS, the following discussion is limited to the most commonly used AAS approved by the US Food and Drug Administration. These are nandrolone
decanoate,\textsuperscript{a} oxandrolone,\textsuperscript{b} oxymetholone,\textsuperscript{c} and stanozolol\textsuperscript{d} (Figure 2).

Nandrolone was synthesized in 1950\textsuperscript{37} and 1953.\textsuperscript{38} Its metabolism is similar to that of testosterone, and its main metabolites are 3-norandrosterone, a 5α derivative, and 2-noretiocholanolone, a 5β derivative.\textsuperscript{39} In vitro studies have shown that nandrolone, like testosterone, can be aromatized.\textsuperscript{40} Despite its similarity to testosterone, nandrolone is more anabolic. The substitution of a hydrogen atom in the C19 methyl group of testosterone creates a new asymmetric center at C10, which may be responsible for the drug's favorable anabolic-to-androgenic ratio.

Oxandrolone, which was synthesized in 1962,\textsuperscript{41} is 17α-alkylated (methyl group), having a reduced C4,5 double bond with a 5α configuration. Oxandrolone's main feature is an oxygen molecule at the C2 position, resulting in a lactone ring. Investigation of oxandrolone metabolism in humans\textsuperscript{42} has shown that 28% of the administered dose is excreted unchanged and ~9% is excreted as 16β-hydroxyoxandrolone glucuronide.

Oxymetholone was synthesized in 1959\textsuperscript{23} and is also 17α-methylated and 5α-saturated. The only structural difference between oxandrolone and oxymetholone is at C2 of the A ring. Whereas

![Figure 2. Structure of the most commonly used anabolic-androgenic steroids in the United States.](image-url)
oxymetholone contains a hydroxymethylene group at C2, oxandrolone has an oxygen at that position. Studies of the metabolism of oxymetholone indicate that the 2-hydroxymethylene group is oxidized to a β-keto-carbonic acid metabolite that is subsequently decarboxylated and 3α-reduced to form 17α-methyl-5α-androstane-3α,17β-diol. Furthermore, several hydroxylated and reduced metabolites in the neutral and basic fractions have been detected but not identified.

The synthesis of stanozolol, the first of a series of anabolically active steroids in which a heterocyclic ring is fused to ring A of the steran skeleton, was reported in 1959. In this compound, which is also 17α-alkylated and 5α-saturated, a pyrazole ring is attached to the A ring. This step is accomplished by condensing oxymetholone with hydrazine. The main excreted metabolites of stanozolol include several hydroxylated byproducts, including 3'-hydroxystanozolol, 3'-hydroxy-17 epistanozolol, 4β-hydroxystanozolol, and 16β-hydroxystanozolol. The major metabolites, including 3'-hydroxystanozolol, 4β-hydroxystanozolol, and 16β-hydroxystanozolol, are all excreted as glucuronide.

A comprehensive review of the biotransformation of testosterone, including phase II metabolism (glucuronidation and sulfatation) of the above AAS, has been published by Schänzer.

MECHANISMS OF ACTION OF AAS

Androgens exert their biological effect through a single intracellular receptor that is present in the reproductive tract as well as in many nonreproductive tissues, including bone, skeletal muscle, brain, liver, kidney, and adipocytes. Some actions of androgens are mediated by local enzymes such as 5α-reductase and aromatase. Synthetic androgens bind to the same receptor as testosterone and DHT.

Anabolic-Myotrophic Effect

The nitrogen-retaining (anabolic) property of androgens was first demonstrated by Kochakian, working alone and with Murlin, in a series of investigations in castrated dogs using urinary extracts, androstenedione, testosterone, and testosterone acetate. Identical results were later reported by Kenyon et al using testosterone propionate in eunuchoid men. Subsequently, a simple technique that uses muscle (eg, the levator ani) or kidney to evaluate the anabolic action of testosterone and uses the ventral prostate or seminal vesicles to evaluate androgenic action has proved useful in ascertaining the anabolic-versus-androgenic effect of many synthetic compounds. The possibility of separating the androgenic and anabolic activities of testosterone was first suggested by Kochakian, who reported that 5α-androstane-3α,17β-diol was more anabolic and less androgenic than testosterone at the same physiologic doses.

In general, most synthetic androgens, including those shown in Figure 2, demonstrate a favorable anabolic-androgenic ratio compared with methyltestosterone, as tested in animal models. Although the relevant experiments were conducted in different laboratories, the results agree with the clinical experience, which indicates that these preparations are less androgenic and more anabolic than methyltestosterone and testosterone esters. However, none of these compounds are devoid of androgenicity.

This partial dissociation of the anabolic and androgenic effects of testosterone in
the synthetic steroids is not the result of differences in the androgenic receptors in muscle compared with those in the reproductive tract. Receptor-binding studies by several investigators have demonstrated that androgenic receptors in skeletal or cardiac muscle exhibit the same binding affinity and biochemical characteristics as those in the reproductive tract. Furthermore, no significant differences have been found in the binding affinities of muscle and prostate androgen receptors for various anabolic steroids. However, comparative binding studies have shown that the number of binding sites per milligram of protein is significantly lower in muscle than in the prostate. Thus, this lower number of androgen-binding sites in muscle compared with reproductive structures may be at least partially responsible for the relatively lower sensitivity of skeletal muscle to androgens.

After puberty, the androgen receptor in striated muscle is downregulated. Consequently, the androgen receptor in skeletal muscle is saturated with physiologic concentrations of circulating testosterone. Whereas the activity of 5α-reductase is markedly low in both skeletal and heart muscle, that of 3α-hydroxysteroid dehydrogenase in converting DHT to a biologically inactive 3α-diol is elevated in these tissues. Thus, the low intracellular concentrations of DHT in muscle is not only the result of low 5α-reductase activity but also of high 3α-hydroxysteroid dehydrogenase activity. Consequently, the main hormones involved in androgen activity in muscle are testosterone and possibly circulating DHT.

In vitro studies have shown that after physiologic concentrations are exceeded, the dose-response relationship between testosterone and the growth of skeletal muscle reaches a plateau. In conjunction with other observations, this finding suggests that at the supraphysiologic levels seen in some athletes, testosterone and synthetic androgens may exert their anabolic action through interaction with glucocorticoid receptors, leading to decreased protein catabolism. Thus, the anabolic action of androgens is mediated directly through androgen-receptor binding and also indirectly by their antiglucocorticoid action.

Several studies in castrated animals have shown that testosterone replacement increases nitrogen retention and muscle mass. Because of a lack of adequate control and standardization, studies on the effect of supraphysiologic doses of testosterone or synthetic androgens on muscle mass in humans have yielded conflicting results. Recently, however, a randomized study by Bhasin et al provided evidence that supraphysiologic doses of testosterone (weekly IM injection of 600 mg testosterone enanthate for 10 weeks) resulted in a significant increase in muscle mass and muscle size and strength in healthy men, particularly when combined with strength training. In another study, these investigators examined body composition and muscle in hypogonadal men before and after 10 weeks of weekly IM administration of 100 mg testosterone enanthate and reported that this therapy resulted in significant increases in weight and muscle mass.

Erythropoietic Effect

It is now established that androgens stimulate erythropoiesis. Administration of androgens to various mammals and fowl increased reticulocyte counts, hemoglobin concentrations, and bone marrow
erythropoietic activity. Conversely, castration of adult male hamsters and rats resulted in decreases in peripheral erythrocyte counts and hemoglobin levels. Anemia in castrated male animals was corrected by administration of androgens.

Several studies in humans have shown higher hemoglobin levels, hematocrit, and erythrocyte counts in adult males compared with adult females. These differences do not appear to be related to iron deficiency, pregnancy, or blood loss. Erythrocyte counts and hemoglobin levels were also higher in healthy men compared with hysterectomized women aged <45 years. Furthermore, hemoglobin concentrations and erythrocyte counts exceed normal values in pathologic conditions associated with excessive androgen production (eg, Cushing's syndrome and congenital adrenal hyperplasia), and frank polycythemia may occasionally be present. Conversely, an appreciable decrease in hemoglobin concentrations and the number of circulating erythrocytes has been noted in patients with hypogonadism, and anemia has been corrected in these patients after the administration of androgens.

A substantial rise in hemoglobin concentrations (eg, ≥21 g/dL) has also been observed in women with breast cancer receiving large doses of androgens. Measurement of erythrocyte mass demonstrated that such increases in hemoglobin concentration were the result of true expansion of the erythrocyte mass and not simply the expression of a relative polycythemia from shrinkage of the plasma compartment. Bone marrow studies in these women revealed marked erythroid hyperplasia, despite advanced metastases within the bone marrow cavity.

The postpuberty increase in hemoglobin concentrations in boys is not limited to the physiologic state. It has been shown that adult males with hereditary hemolytic anemias have notably higher hemoglobin concentrations than do women and children similarly affected. Numerous investigators have suggested that androgens stimulate erythropoiesis by both direct and indirect mechanisms. Administration of androgens to mildly plethoric, exhypoxic polycythemic, or starved rodents resulted in a significant increase in levels of endogenous erythropoietin (EPO). Furthermore, it has been shown that the erythropoietic effect of androgens is completely blocked by injections of antierythropoietin antibody. In humans, elevated levels of erythropoietin have been found in the urine of healthy hypogonadal and anemic subjects after administration of testosterone. The kidneys seem to play an important role in the production of erythropoietin. It is of interest that androgen-treated female rats exhibit renal hypertrophy that closely parallels the increase in erythrocyte mass. In this connection, it has been shown that the ribonucleic acid of the mouse kidney is decreased 40% by castration and increased >100% after administration of androgens. These observations indicate that the erythropoietic response to androgens is in part the result of an increase in erythropoietin production. Without such an increase in erythropoietin, no response to androgen administration is observed.

Similar results in androgen-treated patients with refractory anemia confirm those seen in laboratory animals, in that when erythropoietin values failed to increase markedly, erythrocyte production did not improve despite an adequate level of bone marrow activity. In a study by Alexanian et al, oxymetholone was
given to 28 adults with chronic anemia from bone marrow failure. These investigators noted that the changes in hematocrit and erythrocyte mass were correlated with serial erythropoietin measurements. Erythropoietin excretion was enhanced >5-fold in 16 of 23 evaluable patients (70%). The response was <5-fold in 7 patients, and all patients were unresponsive to oxymetholone.

Experimental data suggest that androgens and certain 5β-H derivatives may also directly enhance erythropoiesis by stimulating erythropoietic stem cells. Using a short-term, serum-free culture supplemented with testosterone and synthetic androgens, Beran et al. compared the efficiency of various androgens in stimulating the growth of erythroid progenitors in the absence of erythropoietin. These investigators found that testosterone and its synthetic derivatives were all able to stimulate the proliferation of erythroid progenitors and, to some extent, myeloid progenitors.

Because many of the AAS tested in vitro undergo significant biotransformation in vivo, the hemopoietic effects observed in vitro may not be applicable to laboratory animals or humans. The results of the foregoing studies emphasizing a direct action of androgens on pluripotential cells confirm the potentiating effects of androgens and explain why testosterone-treated mice were so sensitive to the effect of exogenous erythropoietin. In summary, administration of androgens to humans and laboratory animals has been associated with increased erythropoietin activity and an increased pool of erythropoietin-responsive cells, circumstances that seem ideal for maximum erythropoietic expansion (Figure 3).

**Effect on Erythrocyte 2,3-Diphosphoglycerate**

The function of erythrocyte 2,3-diphosphoglycerate (DPG), an organic phosphate present only in erythrocytes, was unknown until 1967, when Chanutin and Curnish and Benesch and Benesch independently demonstrated its profound effect on the binding of oxygen by hemoglobin. 2,3-DPG decreases hemoglobin-oxygen affinity, facilitating release of oxygen from hemoglobin to tissue. The concentration of 2,3-DPG in normal human erythrocytes is equimolar to that of hemoglobin. In 1972, Parker et al. observed that administration of testosterone enanthate to 6 patients with chronic renal failure receiving biweekly hemodialysis significantly increased 2,3-DPG concentrations in all patients (P < 0.001). After 12 weeks of treatment, the mean 2,3-DPG concentration was 3427 nmol/mL higher than before treatment. Because each 430 nmol/mL of 2,3-DPG results in a 1-mm Hg change in the oxygen half-saturation pressure of hemoglobin (P50) of 2,3-DPG, an increase of this magnitude would correspond to an 8-mm Hg increase in P50. Such a right shift in the oxygen-equilibrium curve would greatly enhance unloading of oxygen to the tissues.

Molinari and Neri administered a single tablet of 50 mg oxymetholone to 8 healthy volunteers, 7 male and 1 female, and measured the level of 2,3-DPG before and 24 and 48 hours after oxymetholone ingestion. They found a statistically significant increase in 2,3-DPG concentrations at both time points (P < 0.05). Significant increases in 2,3-DPG after administration of androgen have also been observed in primates, rats, and mice. This substantial androgen-
induced increase in 2,3-DPG concentrations may play an important role in enhancing performance in athletes using AAS.

Rozenek et al.\textsuperscript{128} studied the endocrine and metabolic responses to resistance exercise in 5 athletes taking AAS and 8 athletes not using these compounds. Athletes in both groups performed similar sets of exercises. Blood samples were collected before and immediately after exercise and after 30 minutes of recovery. Significantly lower lactate concentrations were observed in the athletes using AAS 30 minutes after exercise ($P < 0.015$). Significantly higher hematocrits were observed in the athletes using AAS across all time periods ($P < 0.001$). The lower plasma
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lactate concentrations during recovery observed in those who received AAS may have been due to higher oxygen availability provided by higher erythrocyte mass and/or higher concentrations of 2,3-DPG.

One may ask whether the biological actions of androgens on body mass and erythropoiesis are random and unrelated or intimately orchestrated toward the creation of a better and more efficient fuel (oxygen-delivery system) for an engine with greater horsepower (increased lean body mass). Given that the sole function of erythrocytes is delivery of oxygen to the tissues, it is remarkable that a single hormone not only increases the number of erythrocytes directly and indirectly but also makes them more efficient in delivering oxygen to muscle tissue, whose growth it stimulates. It is possible that enhancement of the oxygen-delivery system and stimulation of muscle mass by androgens are not unrelated side effects of these hormones but an integral part of a complex biological action that has been refined over the course of evolution to provide greater physical strength and endurance (Figure 4).

**Effect on Bone**

Long-standing hypogonadism in adult men has been shown to be associated with reduced bone remodeling, low serum 1,25-dihydroxy vitamin D levels, and decreased bone formation. Androgens stimulate osteoblast proliferation, bone matrix protein production, and synthesis of growth factor and cytokines. All of these effects are mediated by the androgen receptors present on osteoblasts. At puberty, androgens increase cortical thickness through both periosteal and endosteal growth; in addition, they increase trabecular bone formation at epiphyseal sites. It has been demonstrated that bone density correlates positively with serum androgen levels in premenopausal and postmenopausal women. Furthermore, bone mass is positively correlated with muscle mass, which is significantly higher in men than in women.

Androgens antagonize the resorptive effect of parathyroid hormone and interleukin-1 in vitro. The combined trophic action of androgens on bone mass, bone density, and muscle mass is again teleologically understandable, because a larger muscle mass would require the support of a larger, stronger bone mass to ensure maximum strength and uneventful repetitive muscle contraction.

**CLINICAL APPLICATIONS OF AAS**

**Muscle-Wasting Disorders**

There has been considerable recent interest in the therapy of muscle-wasting disorders and cachexia with androgens. In a study by Hengge et al., 30 patients with HIV-related wasting were randomly assigned to receive either oxymetholone (n = 14) or oxymetholone and ketotifen (n = 16). The rationale for combining ketotifen, a histamine antagonist, with oxymetholone was to block the production of tumor necrosis factor-α (TNF-α), which plays an important role in the pathogenesis of muscle wasting and cachexia in HIV-infected patients. The 30 treated patients were compared with a group of 30 untreated individuals who met the trial’s inclusion criteria. All patients received protein and vitamin supplements as well as their regular medication. The investigators found that the body weight of patients receiving oxymetholone in-
Figure 4. Combined effect of androgens on the oxygen delivery system and muscle mass. P50 = oxygen pressure at which 50\% of hemoglobin is oxygen saturated under normal physiologic conditions.
creased dramatically. The average weight gain with oxymetholone alone was 8.2 kg (15%; $P < 0.001$), compared with 6.1 kg in the oxymetholone-plus-ketotifen group (11%; $P < 0.005$). There was a weight loss of 1.8 kg in untreated controls. The time to peak weight was 19.6 weeks with oxymetholone alone and 20.8 weeks with oxymetholone and ketotifen. Quality of life, which was measured on the Karnofsky index, improved equally in both groups after 2 weeks of treatment compared with untreated controls ($P < 0.05$). The addition of ketotifen to oxymetholone did not further increase the amount of weight gain. This agrees with the finding that ketotifen given to HIV-infected patients reduced the release of TNF-α from stimulated peripheral blood mononuclear cells in vitro but not that of TNF-α and soluble-receptor concentrations in plasma.143

Berger et al.144 studied the effectiveness of oral oxandrolone in a double-blind, placebo-controlled study in 63 cachectic HIV-infected patients. Patients were randomly assigned to receive oxandrolone 5 or 15 mg/d for 16 weeks. Patients who received 15 mg/d showed weight gain throughout the 16-week treatment period, whereas those receiving 5 mg/d maintained their weight over 16 weeks. The placebo group showed continued weight loss. Measurable improvement in muscle strength was not noted at the dosages employed in this study. Actual lean body mass was not measured in either of the studies discussed, although because of the nitrogen-retaining ability of oxymetholone and oxandrolone, the weight gains seen in these studies may primarily have reflected an increase in lean body mass. The contribution of other factors such as water retention was not addressed.

In an unblinded study, Gold et al.145 evaluated the effect of 16 weeks of nandrolone decanoate therapy (100 mg IM q2wk) in 24 cachectic HIV-infected men. Patients also engaged in exercise. Both mean body weight and lean body mass increased significantly ($P < 0.05$ and $P < 0.005$, respectively). In a double-blind, randomized, placebo-controlled trial by Strawford et al.146 22 eugonadal men with HIV-associated weight loss were administered testosterone enanthate 100 mg/wk IM to suppress endogenous testosterone production and were randomized to receive oxandrolone 20 mg/d or placebo for 8 weeks (each group, $n = 11$). Both groups also engaged in progressive resistance exercise. Lean body mass was determined by dual x-ray absorptiometry and/or bioelectrical impedance analysis. Both groups showed significant increases in lean body mass, body weight, and strength. Mean gains in each of these variables were significantly greater in the oxandrolone group than in the placebo group ($P < 0.05$, $P < 0.005$, and $P < 0.02–0.05$, respectively).

Bhasin et al.147 administered testosterone enanthate 100 mg/wk IM for 16 weeks to 32 HIV-infected men with low endogenous testosterone levels (<349 ng/dL). Fifteen of the men also engaged in resistance exercise. The results were compared against those in 29 placebo recipients, 15 of whom engaged in exercise. At the completion of the study, body weight had increased by 2.6 kg in men receiving testosterone alone ($P < 0.001$) and by 2.2 kg in men who exercised alone ($P = 0.02$), but did not change in men who received placebo alone. The combination of testosterone and exercise training did not increase body weight to a greater extent than did testosterone alone or exer-
Weight gain was significantly correlated with change in muscle mass, as measured by deuterium oxide dilution ($P < 0.001$). Men treated with testosterone alone, exercise alone, or both experienced significant increases in maximum voluntary muscle strength. Gains in strength in all exercise categories (eg, leg curls, bench press, latissimus pulls) were greater in men assigned to the testosterone-plus-exercise and exercise-alone groups than in those assigned to the placebo-alone group.

In an uncontrolled, randomized study by Sattler et al.,$^{148}$ 30 HIV-positive men with a CD4 count of <400 cells/mm$^3$ were randomly assigned to receive weekly injections of nandrolone decanoate alone or in combination with supervised progressive resistance training 3 times weekly for 12 weeks. Total mean (± SD) body weight increased significantly in both groups (3.2 ± 2.7 kg and 4.0 ± 2.0 kg, respectively; $P < 0.001$), with increases due primarily to augmentation of lean tissue. Mean lean body mass, as determined by dual x-ray absorptiometry, increased significantly more in the group that received progressive resistance training compared with the group that received nandrolone alone (5.2 ± 5.7 kg vs 3.9 ± 2.3 kg, respectively; $P = 0.03$). Body cell mass, determined by bioelectrical impedance, increased significantly in both groups ($P < 0.001$), although between-group differences were not significant. Significant increases in total thigh muscle, quadricep, and hamstring cross-sectional area on magnetic resonance imaging occurred with both treatment strategies ($P < 0.001$). Increases were similar in both groups.

The effectiveness of AAS in increasing lean body mass has been demonstrated in conditions other than HIV that are associated with weight loss. In a study by Johansen et al.,$^{149}$ 29 patients with chronic renal failure undergoing dialysis received nandrolone decanoate 100 mg/wk IM ($n = 14$) or placebo ($n = 15$) for 6 months. Lean body mass increased significantly in patients given nandrolone compared with placebo ($P < 0.001$).

Chronic obstructive pulmonary disease (COPD) is also associated with weight loss. In a double-blind, placebo-controlled study, Ferreira et al.$^{150}$ investigated the effect of oral stanozolol 12 mg/d for 6 months in 23 men with COPD. Treatment was preceded by an IM injection of 250 mg testosterone. All patients received muscle training but no nutritional supplementation. Patients receiving stanozolol showed an increase in mean body weight of 1.8 kg, whereas the control group lost weight ($P < 0.05$). There was also a significant difference in muscle mass between groups ($P < 0.05$).

In a study by Schols et al.$^{151}$ 217 patients with COPD were randomized to receive nutritional intervention alone (420 kcal/d), nutrition plus nandrolone decanoate (50 mg IM for men, 25 mg IM for women), or placebo every 2 weeks for 8 weeks. After 4 and 8 weeks of treatment, patients receiving nutrition alone showed a significant increase in weight due to an increase in fat mass ($P < 0.03$), whereas increased muscle was accompanied by weight gain only in the patients who received nandrolone ($P < 0.03$).

The results of these studies of the short-term effect of AAS in muscle-wasting syndromes demonstrate a substantial beneficial effect of AAS on lean body mass, superior to that achieved with nutritional intervention alone.$^{152,153}$ Although testosterone esters and AAS have proved effective in this setting, the superiority of one preparation over another has not been de-
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terminated. As might be expected, discontinuation of androgen therapy is followed by a reversal of gains in lean body mass. Consequently, it is necessary to determine a minimum effective dose for long-term maintenance therapy in cases of chronic muscle wasting. Consideration must also be given to mode of administration (oral vs injectable) and long-term side effects.

**Damaged Myocardium in Heart Failure**

To explore the effect of androgens on heart muscle, Tomoda\textsuperscript{154} recently evaluated the effect of oxymetholone on residual myocardium of the dilated heart in heart failure. Twelve men with a left-ventricular (LV) diameter of \(>60\) mm (6 with idiopathic dilated cardiomyopathy, 6 with LV volume overload) were administered oxymetholone 5 or 10 mg/d for 3 months. Changes in LV performance were evaluated using echocardiography, and plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were measured. Plasma ANP levels are increased predominantly by atrial distress, whereas increased plasma BNP levels indicate ventricular distress. The results indicated significant improvements in LV dimensions without diastolic dysfunction (\(P < 0.001\)). LV ejection fraction was significantly increased during oxymetholone administration (\(P < 0.05\)). Improvement in the LV contractile state was also suggested by significant reductions in plasma ANP and BNP (both, \(P < 0.005\)). The overall results suggested that administration of a small dose of oxymetholone may have beneficial effects on damaged myocardium. The beneficial effects were similar in patients with cardiomyopathy or volume overload, suggesting the applicability of oxymetholone in both categories of patients.

**Tissue Healing, Malnutrition, and Growth Retardation**

The nitrogen-retaining property of AAS has prompted investigation of their use in the acceleration of tissue healing, as in severe burn injuries,\textsuperscript{155,156} and in the treatment of malnourished patients with alcoholic hepatitis.\textsuperscript{157,158} AAS have also been used to promote growth in children with constitutional retardation of growth and puberty.\textsuperscript{159,160} Oxandrolone at a low dosage of 1.25 to 2.5 mg/d, alone or in combination with growth hormone, has most commonly been used for this purpose. Long-term studies have demonstrated no untoward effect on final adult height. Oxandrolone has also been successfully used in the treatment of Turner’s syndrome,\textsuperscript{161,162} which is associated with significant shortness of stature.

**Bone Marrow Failure Syndromes**

Shahidi and Diamond\textsuperscript{163,164} assessed the use of androgens in the treatment of both acquired and constitutional aplastic anemia. These investigators reported on the treatment with testosterone derivatives (1–2 mg/kg/d) of 17 children with acquired aplastic anemia and 7 children with Fanconi anemia.\textsuperscript{164} Nine of 17 patients in the first group and all 7 patients in the second showed a sustained hematologic response. It is exceedingly rare for patients with these disorders to undergo spontaneous hematologic remission.\textsuperscript{165} The significant masculinization reported in children and women receiving testosterone derivatives subsequently led these and many other investigators to experiment with synthetic
androgens known to have a more favorable anabolic-androgenic ratio.

Allen et al\textsuperscript{166} reported a satisfactory bone marrow and clinical response with oxymetholone, a less-virilizing androgen, in 5 children with aplastic anemia, including 2 whose condition had been refractory to testosterone. In a study by Sanchez-Medal et al,\textsuperscript{167} 69 patients with acquired aplastic anemia were randomly assigned to receive oxymetholone, methanolone, dromostanolone, or methandrostenolone. Overall, therapy with these agents resulted in a 70% remission in all patients, as evidenced by an increase in hemoglobin concentration to $>12$ g/dL and by improvement in numbers of neutrophils and platelets ($P = \text{NS}$). In a multicenter study, Skarberg et al\textsuperscript{168} treated 45 patients with hypoproliferative or aregenerative anemia with oxymetholone for a minimum of 3 months. Thirteen of 18 patients showed partial remission (ie, $\leq 2$ of 3 cell lines [hemoglobin, leukocytes, or platelets] are restored to normal, or counts remain subnormal but the patient ceases to require erythrocyte or platelet transfusions) or full remission.

A 1980 report that administration of antilymphocyte globulin (ALG) and chemotherapeutic agents in preparation for bone marrow transplantation could result in hematologic recovery in aplastic anemia before bone marrow infusion suggested that acquired aplastic anemia might be of autoimmune origin.\textsuperscript{166} This finding led to the use of various immunosuppressive agents, including ALG, antithymocyte globulin (ATG), and cyclosporine, in the treatment of aplastic anemia.

The concept of abrogation of immune-mediated suppression of hematopoiesis through the use of immunosuppressive agents combined with bone marrow stimulants such as androgens gained momentum in the United States and Europe. In a study by Champlin et al,\textsuperscript{170} 26 patients with moderate to severe aplastic anemia received ATG and androgens, and 27 patients received ATG alone. Eleven (42%) patients receiving ATG and androgen responded, compared with 12 (44%) patients receiving ATG alone, a nonsignificant difference. The difference in survival was also not significant (14 [55%] and 14 [50%], respectively). In a subsequent study by Kaltwasser et al,\textsuperscript{171} 30 patients with aplastic anemia were prospectively randomized to receive ATG alone or ATG with methanolone, an oral androgen. Of the 15 patients receiving ATG and methanolone, 11 (73%) responded, including 8 complete responses. In the 15 patients who received ATG alone, 5 (33%) responded, including 2 complete responses. The difference in response rates between groups was statistically significant ($P = 0.01$). The difference in survival rate between the group receiving ATG plus methanolone and the group receiving ATG alone did not reach statistical significance (87% vs 43%). The discrepancy between the results obtained by the 2 sets of investigators cannot be explained, except for the fact that Champlin et al used various androgens rather than just one.

In a study by Bacigalupo et al,\textsuperscript{172} 134 patients with acquired aplastic anemia were randomized to receive ALG and methylprednisolone, with or without oxymetholone. The response rate at 4 months was significantly higher in patients who received oxymetholone compared with those who did not (56% vs 40%; $P < 0.04$). There was, however, no difference in short-term survival. Thus, the use of androgens in the treatment of acquired aplastic anemia remains controversial.
There are, however, patients with acquired aplastic anemia who depend on continuous androgen treatment to maintain adequate blood counts. Azen and Shahidi described 3 cases of patients with acquired aplastic anemia whose blood counts were directly correlated with oxymetholone dosage. To avoid the toxicity of ATG, Shahidi et al treated 23 consecutive children with acquired aplastic anemia with a combination of oxymetholone and cyclosporine. Ten patients had not received previous ATG therapy (group A), and the remaining 13 had not responded to previous ATG therapy (group B). Seven patients (70%) in group A and 5 patients (38%) in group B responded. Eight patients (80%) in group A were alive 5 years after diagnosis, compared with 6 patients (46%) in group B.

The constitutional aplastic anemias comprise a heterogeneous group of pancytopenias, of which Fanconi anemia, an autosomal-recessive syndrome, is the predominant disorder. Patients with this disorder almost invariably develop progressive bone marrow failure, often in childhood. The diagnosis is established by the presence of various congenital anomalies and increased chromosome breakage in lymphocytes cultured in the presence of DNA cross-linking agents such as mitomycin C or diepoxybutane. A hematopoietic stem-cell transplant from a fully matched family member is currently the best treatment for bone marrow failure in these patients. For those who do not have a human leukocyte antigen-identical match, androgens remain the treatment of choice. In 1 report, all 7 patients with Fanconi anemia responded to treatment with androgens. In a larger series, 75% of patients with Fanconi anemia showed evidence of response; overall, the projected median survival age for the 300 androgen-treated patients was 20 years for responders and 14 years for nonresponders.

Among androgen preparations tested over the years, oxymetholone has been recommended as the androgen of choice for the treatment of congenital aplastic anemia. Therapy is initiated at doses ranging from 0.5 to 2 mg/kg per day, and evidence of response is expected in 4 to 8 weeks. In successfully treated patients who achieve a hemoglobin concentration of ~12 g/dL, the dose of oxymetholone is gradually reduced to the minimum effective dose required to maintain a satisfactory hemoglobin concentration (eg, 10–12 g/dL). Modification of the oxymetholone dose is usually based on hemoglobin concentration rather than platelet or leukocyte count.

In a prospective, multicenter study, Hast et al studied the effect of oxymetholone in 11 patients with advanced myelofibrosis. Nine patients showed normalization of or substantial improvement in peripheral blood count after oxymetholone treatment. The need for blood transfusion ceased completely in all 5 patients who had required transfusion before the trial. When oxymetholone treatment was reduced or interrupted, 4 patients relapsed, 2 of whom responded to a renewed course of treatment. Based on this evidence, oxymetholone may be of value in advanced cases of myelofibrosis requiring transfusions.

By virtue of its erythropoietic and, to some extent, myelopoietic action, oxymetholone has been successfully used in a variety of hematologic disorders, including sickle cell anemia, hairy cell leukemia, benzene-induced bone marrow damage, aplastic anemia complicating systemic lupus erythematosus, cyclic neutropenia, refractory anemia type I FAB (French-American-British clas-
sification), and bone marrow failure associated with clonal disorders. In fact, it was recently reported that a 57-year-old patient with trisomy 8 myelodysplastic syndrome responded to oxymetholone and has remained in remission for 11 years while continuing oxymetholone therapy.

**End-Stage Renal Disease**

Before the availability of recombinant human EPO (rHu-EPO), which is currently the main treatment for the anemia of end-stage renal disease, androgens were used with some success in this condition. Because androgens increase the sensitivity of erythroid progenitors to EPO, recent investigations have evaluated the effect on the hematocrit of combined nandrolone and EPO therapy in patients with end-stage renal disease. In their study, Gaughan et al treated patients with nandrolone decanoate for 6 months. The mean (± SD) increase in hematocrit in the group treated with rHu-EPO and nandrolone was significantly greater than that with rHu-EPO alone (8.2% ± 4.4% vs 3.5% ± 2.8%; P = 0.012). Thus, combining androgens with rHu-EPO for the treatment of anemia associated with end-stage renal disease may prove beneficial in patients who require doses of rHu-EPO higher than the recommended 50 to 150 μg/kg 3 times per week to maintain satisfactory hemoglobin concentrations and hematocrit.

**Effect on Plasma Proteins**

Because of their anabolic action, AAS not only increase protein synthesis in muscle but also enhance the production of various circulating proteins, which may be of benefit in several acquired and hereditary disorders. In both COPD and alcoholic hepatitis, administration of androgens has resulted in increases in serum albumin, prealbumin, and transferrin levels.

**Angioneurotic Edema**

Angioneurotic edema, or hereditary angioedema, is a genetically transmitted condition associated with a decrease in or absence of C1-esterase inhibitor, which results in activation of the complement system and leads to cutaneous angioedema, gastrointestinal colic, and/or upper respiratory symptoms of varying frequency and severity. Several reports have indicated that AAS, in particular stanozolol and oxymetholone, significantly benefit patients with this disorder.

In a study by Sheffer et al, daily and alternate-day therapy with small doses of oxymetholone were compared in patients with hereditary angioedema. Fifteen of 16 (94%) patients who experienced at least 1 monthly attack of angioedema became asymptomatic while receiving oxymetholone 5 mg/d. Treatment also resulted in statistically significant mean increases in serum levels of C1-esterase inhibitor (P < 0.001). When 13 patients who had been maintained asymptomatic on oxymetholone 5 mg/d were switched to 5 mg every other day, 7 attacks occurred during a cumulative 50 months of therapy. The adverse effects of daily oxymetholone therapy (depression, elevations in creatine kinase [CK] and alkaline phosphatase levels, menstrual changes, weight gain) largely subsided when patients received alternate-day therapy.

Based on the available data, Cicardi and Agostoni stated in an editorial that at-
tenuated androgens were highly effective and appropriate for long-term prophylaxis against attacks of hereditary angioedema, except in pregnant women and prepubertal patients, and suggested that C1-esterase inhibitor concentrate be reserved for the treatment of unanticipated (in the absence of prodromal symptoms) and dangerous acute attacks of hereditary angioedema.

**Effect on the Coagulation/Fibrinolytic System**

Several 17α-alkylated androgens have been shown to increase plasminogen-activator activity and serum levels of plasminogen, protein C, and antithrombin III. These changes suggest that androgens may protect against thrombosis. However, no such protection has been reported with AAS in controlled trials involving surgical and other high-risk patients. In hereditary antithrombin III and protein C deficiency, administration of androgens has been shown to result in increased levels of these anticoagulant proteins. However, there have been no reports of a decrease in coagulation events with the use of androgens in the absence of concomitant anticoagulant therapy. A decrease in fibrinogen levels has been reported after administration of supra-physiologic doses of androgens. This finding may account for the decreased tolerance to anticoagulants seen in patients receiving AAS therapy.

**ADVERSE EFFECTS**

A major side effect of 17α-alkylated AAS therapy is hepatotoxicity, including elevated levels of liver enzymes, cholestatic jaundice, peliosis hepatis, and various neoplastic lesions. In a recent study, Dickerman et al stated that many reports of hepatic dysfunction secondary to AAS therapy may have been based solely on elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and thus may have overestimated AAS-induced hepatotoxicity. In their study, these investigators found that intensive resistance training in bodybuilders in the absence of any AAS intake leads to elevations in AST, ALT, and CK but not in γ-glutamyl transpeptidase (GGT). For these reasons, they concluded that the evaluation of hepatic function in cases of AAS therapy or abuse should include measurement of CK and GGT levels.

**Cholestatic Jaundice**

The relationship between 17α-alkylated AAS and cholestatic jaundice was first observed >50 years ago in relation to methyltestosterone therapy. Although 17α-alkylation permits oral administration, adverse effects on the liver do not seem to be the result of direct portal access to the liver. Parenteral administration of 17α-alkylated AAS also leads to hepatic dysfunction. Thus, it seems that 17α-alkylation is the main culprit. Testosterone esters and 19-nortestosterone derivatives, which are not 17α-alkylated, have not been associated with jaundice or significant hepatic dysfunction. There is no scientific evidence that other structural differences render any AAS more hepatotoxic than another.

The development of cholestatic jaundice in patients taking 17α-alkylated AAS is predictable and dose and duration related. It occurs rarely and is preventable when the recommended doses of AAS are used. The prognosis is excellent, and, in
the absence of underlying hepatic disease, liver enzyme abnormalities resolve on discontinuation of AAS. Functional liver failure and hepatic necrosis do not occur with 17α-alkylated steroids.212

Laboratory studies of cholestatic jaundice associated with AAS therapy reveal elevations in conjugated bilirubin, AST, and ALT. Alkaline phosphatase levels are normal or modestly elevated in most patients.111,174 It should be noted also that preexisting liver disease such as viral hepatitis and concomitant use of other medications may potentiate or increase the severity of toxicity associated with 17α-alkylated AAS.

In 1 study,174 22 children aged between 2 and 14 years with acquired aplastic anemia were treated with oxymetholone ≤2 mg/kg per day in conjunction with cyclosporine 7 mg·kg per day for a period ranging from 1 month to 3 1/2 years. Two patients treated for the longest period were given oxymetholone and cyclosporine intermittently. No patient developed hyperbilirubinemia or abnormal liver enzyme levels.

In another study,111 18 men and 10 women with chronic refractory anemia were treated with oxymetholone 5 and 1 mg/kg per day, respectively. Twenty-six patients were treated for at least 3 months. Two patients in the 5-mg/kg group developed hyperbilirubinemia and elevated liver enzymes. All values returned to normal 2 months after cessation of therapy.

Peliosis Hepatis

Peliosis hepatis, a rare side effect of AAS therapy, consists of multiple small hemorrhagic cysts distributed randomly in the liver parenchyma. Cases have been reported in ~60 recipients of AAS.216-219 The exact mechanism by which AAS cause peliosis hepatis remains unknown and may be separate from the hepatic dysfunction induced by 17α-alkylated steroids. Testosterone, which is not 17α-alkylated and exerts no adverse effect on liver function, has also been reported to cause peliosis hepatis.220

Hepatic Neoplasms and Carcinoma

Hepatic neoplasms, which can be benign or malignant, have been reported in recipients of 17α-alkylated AAS. A causative relationship has been suggested by reports of regression of some lesions on discontinuation of therapy.221 Among benign lesions, diffuse hyperplasia, nodular regenerative hyperplasia, and focal nodular hyperplasia have been attributed to 17α-alkylated AAS.213

A more serious adverse effect of AAS therapy is hepatocellular carcinoma. Recant and Lacy222 were the first to report the association between AAS and hepatocellular carcinoma. One of the common features in cases of AAS-induced hepatocellular carcinoma has been the long duration of therapy and the high dosage used. In a 1987 report, Ishak and Zimmerman213 estimated that of some 40 patients with AAS-induced hepatocellular carcinoma reported in the literature, all had been taking AAS for 2 to 4 years, with 11 years the longest recorded period.

More recently, Kosaka et al223 reviewed the history of 13 patients with AAS-induced hepatocellular carcinoma in Japan. In 12 patients, the total dose of androgens ranged from 12 g taken over 7 years to 179 g taken over 12 years. The 1 remaining patient had taken a total of 200 mg of fluoxymesterone over 2 months. This patient and a patient who received a total...
AAS dose of 12.5 g were hepatitis C and hepatitis B positive, respectively. It is interesting that hepatocellular carcinoma occurred in 1 patient who received only methanolone, a non-17α-alkylated steroid, for 4 years at a total dose of 14 g. In general, the average interval between initiation of oral AAS therapy and the occurrence of hepatocellular carcinoma has been estimated at 72 months, but the interval may be considerably shorter in patients with Fanconi anemia.

Some of the features of hepatocellular carcinoma associated with 17α-alkylated AAS therapy have cast doubt on the malignant nature of these lesions, including the rarity of elevated alpha-fetoprotein levels, the benign course of the disorder in many cases, the rarity of metastases, and, above all, the marked regression of the tumor after withdrawal of medication.

Clinical experience suggests that to avoid or minimize hepatotoxicity in patients receiving long-term AAS therapy, such baseline studies as liver function tests, a hepatitis panel including polymerase chain-reaction testing for hepatitis C, computed tomography of the liver, and ultrasonography are essential to rule out the possibility of any preexisting liver pathology. During therapy, liver function testing is desirable every 2 to 3 months and liver imaging every 5 to 6 months.

**Local and Systemic Adverse Effects of Injectable Androgens**

Because the non-17α-alkylated androgens such as nandrolone decanoate and testosterone esters must be administered by deep IM injection, there have been numerous instances of local reactions such as bacterial and fungal abscesses and exuberant local tissue reactions. In addition, transmission of hepatitis B and C and HIV among heterosexual male bodybuilders who share needles has been reported.

**Virilizing Effects**

Depending on the dose, all AAS result in mild or significant masculinization in women and children. In cases in which large doses of AAS have been prescribed, deepening of the voice, hirsutism, acne, and clitoral/phallic enlargement have been observed. In females of menstruating age, amenorrhea, hair loss, and changes in libido are common. Significant water retention may also occur. In general, virilization is more common with testosterone esters. Nandrolone decanoate, a long-acting AAS in which the 17-hydroxy is esterified with a long-chain fatty acid, may occasionally result in substantial water retention. In the author’s experience, use of oxymetholone in patients with constitutional or acquired aplastic anemia at the recommended dosage is not associated with significant masculinization in children or women.

**Premature Closure of Epiphysis**

Another concern often cited in the literature is androgen-induced premature closure of the epiphysis in children, resulting in a reduction in ultimate height. In 1956, Sobel et al reported on the use of methyltestosterone as a growth stimulant in children, noting a considerable increase in the rate of skeletal maturation and a significant discrepancy between height age and bone age. However, this effect has not been reported with AAS; in fact, AAS can increase height without significantly affecting bone age. In a double-blind, placebo-controlled study, Keele and...
Worley examined the effects of oxymetholone on growth in 25 children with growth retardation and compared the results with those obtained in 29 children who received placebo. After 12 months, the mean increase in height was significantly greater in the oxymetholone group compared with the placebo group ($P < 0.02$). There were no significant between-group differences in bone age.

**Psychiatric and Behavioral Effects**

The psychiatric adverse effects of anandrogens have been reviewed by Uzych. Available data concerning the possible effects of AAS on libido in men and women and the way in which they affect libido differently in men and women are often inconsistent or inconclusive. AAS may both relieve and cause depression. Cessation or diminished use of AAS may also result in depression. Testosterone levels appear to be positively associated with aggressive behavior, particularly in response to provocation. Various psychotic symptoms and manic episodes may also be associated with AAS. Hypomania induced by synthetic androgens is also possible.

**Effects on Serum Lipid Levels**

Several studies have shown that AAS therapy results in significant depression of high-density lipoprotein cholesterol (HDL-C) levels ($P < 0.001–0.05$), while raising levels of low-density lipoprotein cholesterol (LDL-C). In a review by Glazer, the percentage decrease in plasma HDL-C levels in 15 studies ranged from 39% to 70%. In 1 of the studies reviewed, the relationship between AAS dose and HDL-C depression was investigated at drug doses ranging from 0.8 to 27.75 times the maximum recommended dose for the treatment of androgen deficiency. The extent of HDL-C depression did not correlate with AAS dosage. The results of other studies reviewed also indicated that in general, there was minimal to no dose relationship in AAS-induced depression of HDL-C levels.

AAS lower HDL-C levels primarily by induction of the HDL-catabolizing enzyme hepatic triglyceride lipase (HTGL), which is 1 of 2 heparin-elutable lipolytic enzymes in plasma (the other is lipoprotein lipase). HTGL is localized to the luminal surface of hepatic endothelium and presumably catabolizes HDL via its phospholipase activity. During AAS therapy, HTGL activity has been reported to show a statistically significant increase ($P < 0.001$).

Several studies have also shown a statistically significant AAS-induced elevation in LDL-C levels ($P < 0.001–0.05$). Attempts to deduce a dose relationship yielded conflicting results.

As might be expected, alterations in serum lipids during AAS therapy are reversed on discontinuation of treatment. In general, it takes ~1 month after cessation of therapy for lipid profiles to return to baseline values.

**Other Side Effects**

Other side effects have been reported in patients receiving AAS therapy, including glucose intolerance and insulin resistance. However, the onset of diabetes has not been documented. The suppression of pituitary gonadotrophins by AAS leads to hypogonadism, as evidenced by decreased circulating testosterone levels. Testicular atrophy and impaired spermatogenesis have also been reported.
CONCLUSIONS

To minimize or avoid serious toxicities with AAS therapy, close medical supervision and periodic monitoring are important, with dose adjustment as appropriate to achieve the minimum effective dose. Considering the biological effects and potential adverse effects of AAS, administration of these agents should be avoided in pregnant women, women with breast cancer or hypercalcemia, men with carcinoma of the prostate or breast, and patients with nephrotic syndromes or significant liver dysfunction.

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