Position Stand on Androgen and Human Growth Hormone Use

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Abstract

Hoffman, JR, Kraemer, WJ, Bhasin, S, Storer, T, Ratamess, NA, Haff, GG, Willoughby, DS, and Rogol, AD. Position stand on Androgen and human growth hormone use. *J Strength Cond Res* 23(5): S1–S59, 2009–Perceived yet often misunderstood demands of a sport, overt benefits of anabolic drugs, and the inability to be offered any effective alternatives has fueled anabolic drug abuse despite any consequences. Motivational interactions with many situational demands including the desire for improved body image, sport performance, physical function, and body size influence and fuel such negative decisions. Positive countermeasures to deter the abuse of anabolic drugs are complex and yet unclear. Furthermore, anabolic drugs work and the optimized training and nutritional programs needed to cut into the magnitude of improvement mediated by drug abuse require more work, dedication, and preparation on the part of both athletes and coaches alike. Few shortcuts are available to the athlete who desires to train naturally. Historically, the NSCA has placed an emphasis on education to help athletes, coaches, and strength and conditioning professionals become more knowledgeable, highly skilled, and technically trained in their approach to exercise program design and implementation. Optimizing nutritional strategies are a vital interface to help cope with exercise and sport demands (516–518). In addition, research-based supplements will also have to be acknowledged as a strategic set of tools (e.g., protein supplements before and after resistance exercise workout) that can be used in conjunction with optimized nutrition to allow more effective adaptation and recovery from exercise. Resistance exercise is the most effective anabolic form of exercise, and over the past 20 years, the research base for resistance exercise has just started to develop to a significant volume of work to help in the decision-making process in program design (187,248,305). The interface with nutritional strategies has been less studied, yet may yield even greater benefits to the individual athlete in their attempt to train naturally. Nevertheless, these are the 2 domains that require the most attention when trying to optimize the physical adaptations to exercise training without drug use. Recent surveys indicate that the prevalence of androgen use among adolescents has decreased over the past 10–15 years (154,159,246,253,370,441,493). The decrease in androgen use among these students may be attributed to several factors related to education and viable alternatives (i.e., sport supplements) to substitute for illegal drug use. Although success has been achieved in using peer pressure to educate high school athletes on behaviors designed to reduce the intent to use androgens (206), it has not had the far-reaching effect desired. It would appear that using the people who have the greatest influence on adolescents (coaches and teachers) be the primary focus of the educational program. It becomes imperative that coaches provide realistic training goals for their athletes and understand the difference between normal physiological adaptation to training or that is pharmaceutically enhanced. Only through a stringent coaching certification program will academic institutions be ensured that coaches that they hire will have the minimal knowledge to provide support to their athletes in helping them make the correct choices regarding sport supplements and performance-enhancing drugs.

The NSCA rejects the use of androgens and hGH or any performance-enhancing drugs on the basis of ethics, the ideals of fair play in competition, and concerns for the athlete's health. The NSCA has based this position stand on a critical analysis of

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the scientific literature evaluating the effects of androgens and human growth hormone on human physiology and performance. The use of anabolic drugs to enhance athletic performance has become a major concern for professional sport organizations, sport governing bodies, and the federal government. It is the belief of the NSCA that through education and research we can mitigate the abuse of androgens and hGH by athletes. Due to the diversity of testosterone-related drugs and molecules, the term androgens is believed to be a more appropriate term for anabolic steroids.

1. Androgen administration in a concentration-dependent manner increases lean body mass, muscle mass, and maximal voluntary strength in men. However, the upper concentration for maximum effects remains unknown.
2. Combined administration of androgens and resistance exercise training is associated with greater gains in lean body mass, muscle size, and maximal voluntary strength in men than either intervention alone.
3. Testosterone therapy is approved only for the treatment of hypogonadism in adolescent and adult men. However, the anabolic applications of androgens and selective AR modulators are being explored for the functional limitations associated with aging and some types of chronic illness.
4. The magnitude and frequency of adverse effects among androgen users have not been systematically studied. Potential adverse effects of androgen use in men include suppression of the hypothalamic-pituitary-gonadal axis, mood and behavior disorders, increased risk of cardiovascular disease, hepatic dysfunction with oral androgens, insulin resistance, glucose intolerance, acne, gynecomastia, and withdrawal after discontinuation. In addition, the polypharmacy of many androgen users (psychoactive and accessory drugs) may have serious adverse effects of their own.
5. The adverse effects of androgen administration in women are similar to those noted in men. In addition, women using androgens may also experience virilizing side effects such as enlargement of the clitoris, deepening of the voice, hirsutism, and changes in body habitus. These changes may not be reversible on cessation of androgen use.
6. In pre- and peripubertal children, androgen use may lead to virilization, premature epiphyseal closure, and resultant adult short stature.
7. Since 1990, the use of androgens for a nonmedical purpose is illegal. Androgens are labeled as a schedule III drug. Possession of any schedule III substance including androgens is punishable by fine, prison time, or both. Prescribing androgens for bodybuilding or enhanced athletic performance is also punishable as noted above.
8. Human growth hormone increases lean body mass within weeks of administration; however, the majority of the change is within the water compartment and not in body cell mass.
9. Human growth hormone is unlikely to be administered as a single agent but often in combination with androgens.
10. Combined administration of hGH and resistance exercise training is associated with minimal gains in lean body mass, muscle size, and maximal voluntary strength in men compared with resistance exercise alone.
11. Human growth hormone is approved for the therapy of children and adolescents with growth hormone deficiency, Turner syndrome, small for gestational age with failure to catch-up to the normal growth curves, chronic kidney disease, Prader-Willi syndrome, idiopathic short stature, Noonan syndrome, and *SHOX* gene deletion. For adults, hGH is approved for the treatment of GH deficiency, AIDS/HIV with muscle wasting, and short bowel syndrome.
12. The magnitude and frequency of adverse events associated with hGH use are clearly dose related. Potential adverse events include suppression of the hypothalamic-pituitary GH/IGF-1 axis, water retention, edema, increased intracranial pressure, joint and muscle aches, and those of needle injection (hepatitis and HIV/AIDS). These should be the same in women as well as in men.
13. Continued effort should be made to educate athletes, coaches, parents, physicians, and athletic trainers along with the general public on androgen and hGH use and abuse. Educational programs should focus on potential medical risks of these illegal performance-enhancing drugs use, optimizing training programs and concurrent nutritional strategies to enhance physiological adaptation and performance. In addition, educating coaches on setting realistic training goals and expectations for their athletes will help reduce the pressures to use illegal PED and assist in potentially identifying potential users of illegal PED.
14. The NSCA supports and promotes additional research funding to be directed toward effective educational programs, documentation of both acute and long-term adverse effects of androgen and hGH abuse, strategies for optimizing athletic performance through training and nutritional interventions, strategies to help athletes discontinue androgen and hGH use, and strategies for the detection of abuse of androgens and hGH.

The use of androgens by athletes has received a lot of attention in the media over the past decade. The current media attention to this topic has falsely suggested that androgen use by athletes is a relatively new phenomenon. It contrast, it is something that has been around for many decades. For the past half century, the use of androgens by athletes has increased medical and scientific focus on the efficacy and dangers of these compounds. The medical risks associated with androgens as well as ethical considerations have led the major sport governing bodies to initiate measures to combat their use. All major national and international sport organizations have banned androgens from use by their athletes, and detection of use results in suspension from

competition. Although educational and awareness programs have been developed to combat the use of androgens, the efficacy of these programs is not clear. Considering that most athletes and coaches are aware of the potential side effects and risks associated androgens use, including the risk of becoming barred from competition, they still continue to search for ways to mask their use to avoid detection or have redirected their efforts to use anabolic drugs that are not detectable (e.g., human growth hormone [hGH]).

A number of position stands and review papers have been written on this subject. However, the information contained in these reviews is often outdated, incorrect, or incomplete. Previous position stands published by the National Strength and Conditioning Association (NSCA) and the American College of Sports Medicine (ACSM) are more than 15–20 years old. In light of the intense media scrutiny that has been recently focused on these performance-enhancing drugs, it appears that an updated review and examination of this issue are required. It is acknowledged that there are other performance-enhancing drugs that are presently being used by athletes (e.g., erythropoietin [EPO], insulin, thyroid hormone). However, this report will focus on the most widely publicized drugs: androgens and hGH. The important clinical use of these drugs will be discussed as well. Each of these drugs will be examined separately, with specific emphasis on their physiological role, history of use, research on the efficacy as a performance-enhancing drug, medical issues associated with their use, and when applicable, dosing patterns, frequency of use, detection methods, masking agents, and other drugs that are commonly used concomitantly with these anabolic agents. In addition, legal issues associated with these performance-enhancing drugs, direction of future research, and performance-enhancing drug education programs will be discussed.

Androgens

Androgen is a sex hormone that promotes the development and maintenance of the male sex characteristics. Testosterone is the principal secreted androgen in men. Androgens have both masculinizing (development of male secondary sex characteristics, including hair growth) and anabolic effects (increase in skeletal muscle mass and strength). For decades, pharmaceutical companies have attempted to develop androgens that have preferential anabolic activity and reduced or no androgenic (masculinizing) activity; these compounds have been referred to as anabolic steroids. However, there are few clinical trial data in humans to support the view that such compounds are purely anabolic; the steroidal compounds available to date have both androgenic and anabolic activities. A number of terms–anabolic steroids, androgenic steroids, anabolic-androgenic steroids, and androgens–have been used in literature to describe these androgen derivatives. For the sake of uniformity and accuracy, we have used the term "androgen" to describe these compounds that bind androgen receptor (AR) and exert masculinizing as well as anabolic effects to varying degrees.

What Is the Physiological Role of Testosterone?

Testosterone is a 19-carbon steroid (Figure 1) with a ketone group at position 3, hydroxyl group at position 17, and a double bond at position 4. Its basic structure is composed of 3 cyclohexane rings and 1 cyclopentane ring with a methyl group at positions 10 and 13 (472). The biosynthesis of testosterone begins in the adrenal cortex where cholesterol is converted through a multistep process to dehydroepiandrosterone (DHEA) and androstenedione. The androgens androstenediol and androstenedione are natural testosterone precursors. The biosynthesis of testosterone takes place within the testicular Leydig cells in 2 metabolic pathways. During the progesterone pathway (delta-4 pathway), pregnenolone is metabolized to progesterone by the 3-beta-hydroxysteroid dehydrogenase and an isomerase. Progesterone is then converted to 17-alpha-hydroxyprogesterone by 17-alpha-hydroxylase and C17:C21-lyase to androstenedione, then to testosterone by reduction of the 17-keto group by 17-beta-hydroxysteroid dehydrogenase. The DHEA pathway (delta-5 pathway) leads from pregenolone to 17-alpha-hydroxypregnenolone to DHEA and is then converted to 5-delta-androstenediol by C17:C21-lyase.

Testosterone and the other C-19 androgens can also be converted into the compound dihydrotestosterone (DHT) or into estradiol by the action of the enzyme aromatase (Figure 2). In males, more than 95% of testosterone is secreted by the Leydig cells under the control of luteinizing hormone (LH). The remainder is produced via conversion in the adrenal cortex. This is a major way in which females produce testosterone in addition to the ovaries (although testosterone concentrations are much lower in women). Healthy men produce approximately 4.0–9.0 mg of testosterone per day with blood concentrations ranging from 300 to 1,000 $ng \cdot dL^{-1}$ (10.4–34.7 $nmol \cdot L^{-1}$), whereas for females blood concentrations range from 15 to 65 $ng \cdot dL^{-1}$ (0.5–2.3 $nmol \cdot L^{-1}$) (38,59). Dihydrotestosterone is mostly formed via peripheral conversion in other target (non-skeletal muscle) tissues via the enzyme 5α-reductase, an enzyme that converts testosterone to DHT in the cytoplasm. Once secreted, testosterone travels through the circulation either free (i.e., free testosterone) or bound to a carrier protein. About 35–38% of testosterone travels bound to albumin, with the remaining bound to the glycoprotein sex hormone–binding globulin (SHBG) (472). According to the free hormone hypothesis, it is only the free testosterone that is bioavailable and able to diffuse through the cell membrane and bind to its cytosolic receptor, or perhaps bind to some membrane receptor (414). However, recent evidence that SHBG-bound testosterone may also be internalized through the megalin family of proteins and be biologically active (225,367). There is a growing body of evidence that albumin-bound testosterone may dissociate in many organs such as the liver and brain and become

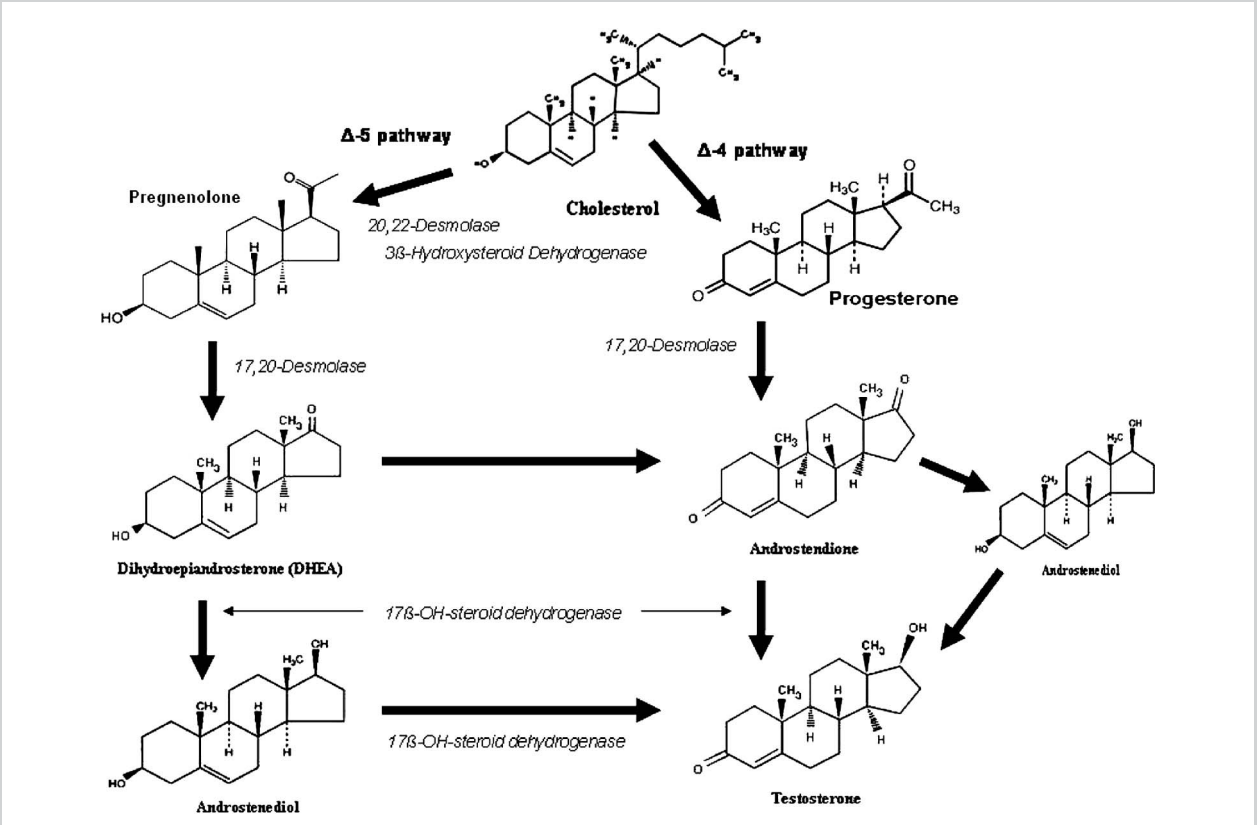


Figure 1. Testosterone synthesis.

biologically available (356,432). Only about 0.5–2.5% of circulating testosterone is in the free form. Thus, free testosterone concentration is a function of total testosterone concentration and binding protein concentration. Testosterone plays a number of important roles in the human body. Testosterone affects many physiological systems, which are listed in Table 1. It is believed that most actions of testosterone are dependent on total circulating concentrations and directly produced via testosterone's interaction with the AR. The increase in gene transcription and translation of proteins elicits several changes that enhance muscle hypertrophy, strength, endurance, and power (285,287,458). In addition, testosterone has been suggested to lead to muscle anabolism via antiglucocorticoid actions (i.e., testosterone may bind with high affinity to cortisol receptors, thereby attenuating potential catabolic actions or inhibit glucocorticoid action via cross-regulation with ARs), potentiation of muscle insulin-like growth factor-1 (IGF-1), and attenuation of myostatin action and signaling (38,285,546). Last, testosterone plays a key role in development of secondary sex characteristics, for example genital growth during puberty, deepening of the voice, hair growth, and so on.

Feedback Control of Testosterone Synthesis and Secretion. Control of testosterone synthesis and secretion begins in the hypothalamus, which links the nervous and endocrine systems and secretes several regulatory hormones that act on the anterior pituitary gland to either increase or inhibit hormonal release. One hormone secreted by the hypothalamus is gonadotropin-releasing hormone (GnRH). Gonadotropin-releasing hormone is secreted in pulses every 90–120 minutes and binds to gonadotropes in the anterior pituitary where it stimulates the secretion of LH. Luteinizing hormone secreted into circulation binds to receptors on Leydig cells of the testes where it stimulates testosterone secretion. Testosterone elevations, via negative feedback, eventually will reduce further testosterone secretion via direct inhibition at the hypothalamic and anterior pituitary axis. Much of the inhibition stems from peripheral aromatization of testosterone to estradiol. Estradiol elevations feedback directly to the hypothalamus, thereby reducing secretion of GnRH and subsequently LH from the anterior pituitary. Androgens use negative feedback on the hypothalamic-pituitary axis such that the body's own endogenous testosterone production is minimized. Thus, during exogenous androgen use, testicular shrinkage may ensue. The adverse effects associated with androgen use have prompted many athletes to use endogenous testosterone enhancers when coming off of androgen cycles. This will be discussed in more detail later in this report.

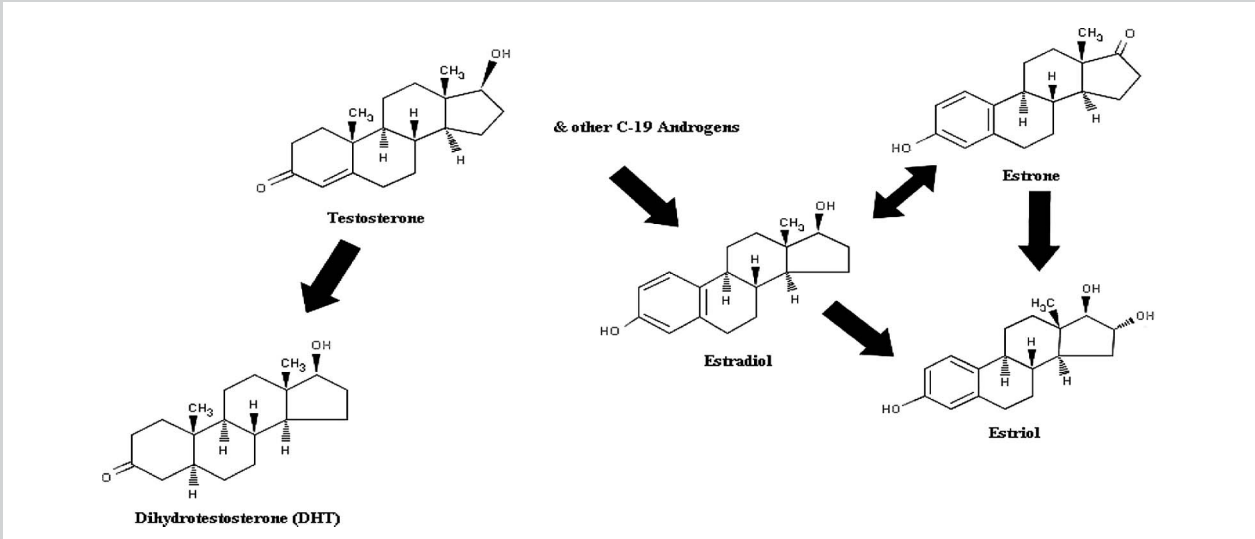


Figure 2. Basic synthesis of dihydrotestosterone and the estrogens: estradiol, estrone, and estriol.

Mechanisms of Testosterone Effects on the Skeletal Muscle. Testosterone-induced increase in skeletal muscle mass is associated with hypertrophy of both type I and type II fibers (470) and an increase in the number of myonuclei and satellite cells (491). Testosterone promotes the differentiation of mesenchymal multipotent cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage (515,532). Androgens regulate mesenchymal multipotent cell differentiation by binding to AR and promoting the association of AR with β-catenin and translocation of the AR–β-catenin complex into the nucleus, resulting in activation of T-cell factor 4 (TCF-4) (548). The activation of TCF-4 modulates a number of Wnt-regulated genes that promote myogenic differentiation and inhibit adipogenic differentiation (548).

Testosterone also inhibits preadipocyte differentiation into adipocytes (548). The effects of testosterone on myogenic differentiation in vitro are blocked by the AR antagonist, bicalutamide, indicating that these effects are mediated through an AR pathway (548). It is possible that androgens might exert additional effects through nongenomic mechanisms. Testosterone increases fractional muscle protein

Table 1. General effects of androgens in non–sex-linked tissues.

- Increases lean body mass
- Increases cardiac tissue mass
- Decreases body fat percentage
- Increases isometric and dynamic muscle strength and power
- Enhances recovery ability between workouts
- Increases protein synthesis, accretion, and nitrogen retention (and possible anticatabolism)
- Increases muscle cross-sectional area
- Stimulates growth of the epiphyseal plate
- Increases erythropoiesis, hemoglobin, and hematocrit
- Increased vasodilation
- Increases bone mineral content, density, and markers of bone growth
- Regulation of osteoblasts, bone matrix production, and organization
- Increases glycogen and creatine phosphate storage
- Increases lipolysis and low-density lipoproteins and decreases high-density lipoproteins
- Increases neural transmission, neurotransmitter release, myelinization, and regrowth of damaged peripheral nerves
- Repression of myostatin
- Behavior modification (i.e., aggression)
- Acute elevations in skeletal intramuscular calcium concentrations

synthesis and improves the reutilization of amino acids by the muscle (448,506).

Androgen Receptor. Classical genomic actions of androgens are mediated through the AR. The AR gene is located on the long q arm of chromosome X at position 11–12 and contains 8 exons coding for the N-terminus, central DNA binding, and C-terminal ligand-binding domains (199,375). The first exon contains several regions of repetitive DNA sequences including the CAG triplet repeats (313). The length of this sequence is variable and long CAG repeats interfere with androgen actions, whereas short repeats enhance androgen action. The AR is a 110-kDa receptor consisting of 919 amino acids, 12 α-helices, and 2 β-sheets that belong to a large family of nuclear transcription factors. A truncated AR protein (87 kDa) with similar function has also been identified (532). Studies have shown that ARs are located in virtually all tissues except in the spleen and adrenal medulla (393,491).

Free testosterone diffuses through the cell membrane and binds to the C-terminal ligand-binding domain, causing dissociation of the AR from a group of heat shock proteins in the cytoplasm. Testosterone binding to AR results in conformational changes in the AR protein, recruitment of tissue-specific coregulators, and translocation of liganded complex into the nucleus where it binds the androgen response elements of AR target genes (161,548). Considering that skeletal muscle contains little 5α-reductase, testosterone is the primary ligand (not DHT) inducing transcription. In addition, the N-terminal region is the primary site for interaction with large families of coregulators that function to amplify the transcriptional signal and mediate AR action (157). Coregulator binding forms a bridge between the DNA-bound AR and the transcriptional machinery, thereby modulating transcription and tissue selectivity. Approximately 300 coregulators have been identified (523).

Androgen binding stabilizes the AR (547,548). The half-life of AR without androgen binding is 1 hour, whereas the AR-androgen complex extends the half-life to 6 hours (287). Androgens slow AR degradation by prolonging nuclear retention. Testosterone (the primary androgen interacting with ARs in skeletal muscle) dissociates from the AR 3 times faster than DHT or synthetic androgens and is less effective for stabilizing the AR (547). However, similar stabilizing effects occur with larger doses of testosterone in comparison with lesser dosages of DHT (287,547). Thus, it appears AR stabilization is dose dependent. The AR is capable of undergoing multiple bouts of recycling between the nucleus and the cytoplasm after ligand binding and dissociation (427). Upregulation of AR content is affected by other hormone-receptor interactions including IGF-I, growth hormone (GH), and triiodothyronine, whereas glucocorticoids and estrogens downregulate AR messenger RNA (mRNA) (97,161,169,322,419).

The AR concentration in skeletal muscle depends on several factors including fiber type, contractile activity (e.g., resistance training), nutritional supplementation, and the concentrations of testosterone (31,84,155,307,415). Resistance training upregulates AR content within a few days after a workout (31). However, the initial response may be downregulation (415) unless nutritional (e.g., protein, carbohydrate) interventions are applied (307). The regulation of AR mRNA by androgens varies with androgen dose duration and mode of administration (16,169,306,308,331,355,380,448). Long-term exposure to high concentrations of androgens may downregulate AR content in some tissues (83).

Nongenomic Actions of Testosterone. Although most actions of testosterone are mediated within the cytoplasm via the AR, some studies have suggested that some rapid actions of testosterone (i.e., that take place within seconds or minutes) may be mediated via nongenomic activity (414). Evidence supporting nongenomic actions has been attained from studies showing these actions of testosterone to occur despite either cytosolic AR inhibition or administration of a testosterone molecule unable to diffuse across the cell membrane (170). For example, nongenomic actions of testosterone have been identified to occur in Sertoli cells, hypothalamus, anterior pituitary, prostate, osteoblasts, immune cells, cardiovascular tissues, and skeletal muscle (170,414). In skeletal muscle, testosterone administration has been shown to rapidly (within minutes) increase intramuscular calcium and extracellular signal–regulated kinase 1/2 (ERK 1/2) phosphorylation (a class of mitogen-activated protein kinase and an intermediate involved in muscle hypertrophy) (170). Similar intramuscular calcium increases have been reported in cardiac myocytes after testosterone administration (515). It has been suggested that these nongenomic actions of testosterone may be mediated by a membrane-bound AR (coupled to a G-protein–linked second messenger system) (170) or perhaps by a membrane-bound SHBG receptor for non–free testosterone still bound to SHBG (414). However, a membrane receptor for testosterone has not yet been isolated and the evidence for nongenomic actions remains inconclusive.

Testosterone Metabolism. In addition to peripheral conversion to DHT and estradiol, testosterone is inactivated by the liver and excreted in urine via 2-phase metabolism. In phase 1 metabolism, the liver converts most circulating testosterone (and other androgens) to various inactive metabolites via enzymatic oxidation, reduction, and hydroxylations to the A, B, C, and D rings (437). The major urinary metabolites of testosterone, androsterone and etiocholanolone, are formed via the enzyme 17β-hydroxy dehydrogenase and are excreted as 17-ketosteroids. Phase 2 reactions in the liver and/or kidneys include conjugation of phase 1 metabolites with either glucuronic acid or sulfuric acid. Conjugation reactions are enzymatically controlled (e.g., UDP-glucuronosyltransferase enzymes) (48). Not all androgens are excreted as conjugates, some are unconjugated including oxandrolone and some metabolites of stanozolol (437).

Detection of androgens or their metabolites in the urine is the basis of current drug testing.

Types of Androgens

Testosterone, when administered orally, has a short half-life because of its first-pass presystemic metabolism. 17-Alpha alkyl substitutions in the testosterone molecule render it less susceptible to first-pass presystemic metabolism. However, 17-alpha alkylated derivatives are potentially hepatotoxic and markedly suppress high-density lipoprotein (HDL) cholesterol levels. They are not recommended for clinical use.

Esterification of the 17-beta-hydroxyl group renders the molecule more hydrophobic; testosterone esters such as cypionate, undecanoate, and enanthate, when injected in an oily suspension intramuscularly, are released slowly from the hydrophobic oil depot into the general circulation, thus extending their duration of action. The degree of hydrophobicity is related to the length of the ester side chain; the longer esters such as cypionate and enanthate have more extended duration of action than shorter esters such as propionate. The de-esterification of testosterone esters is not rate limiting; thus, the plasma half-life of testosterone esters is not significantly different from that of unesterified testosterone. The long duration of action of testosterone esters is mostly due to the slow release of the testosterone ester from the oily depot in the muscle.

Slight biochemical modifications can alter biological activity by modifying presystemic metabolism, half-life, AR binding affinity, AR stabilization, coactivator recruitment, nuclear translocation, DNA binding affinity, and tissue selectivity. Also, biochemical modifications may determine whether the resulting molecule can undergo aromatization or 5-α reduction. Only a limited amount of information is available about the structure-activity relationships of the testosterone molecule.

One of the first changes made to the testosterone molecule was the addition of a methyl or ethyl group to the 17-alpha-carbon position. This addition inhibits the presystemic metabolism of the molecule, greatly extending its half-life and making it active when administered orally. However, orally administered 17-alpha alkylated androgens are potentially hepatotoxic and markedly lower plasma HDL cholesterol. 17-Alkyl substitution also lowers the interaction with aromatase (148).

Because there are many agents in production and literally hundreds more that have been synthesized, this discussion focuses on the basics involving the steroid ring substitutions and how these substitutions affect the properties of the drug. Detailed analysis is limited to those agents that are available or have been approved for use in the U.S.A. Table 2 provides specific structure and chemical information on selected, popular androgens (AAS).

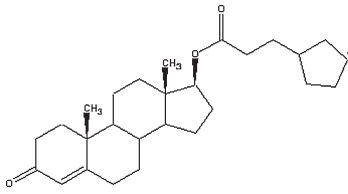
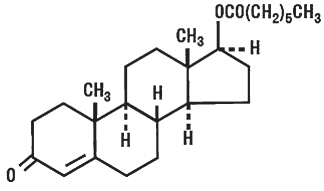
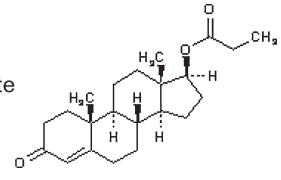
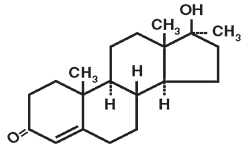
Testosterone Esters. Testosterone esters have seen an increase in their use in replacement therapy and in their propensity for abuse. The testosterone esters all have the testosterone molecule with a carboxylic acid group (ester linkage) attached to the 17-β hydroxyl group in common. These esters differ in structural shape and size and function only to determine the rate at which the testosterone is released from tissue. Larger esters are released into the bloodstream more slowly, as the ester decreases the solubility of the steroid in water and increases its fat solubility. When a steroid has an ester attached, the steroid is rendered inactive because the ester prevents it from binding to a receptor. For the steroid to become active again, the enzyme esterase must detach the ester and restore the hydrogen to form the hydroxyl group attached to C-17. Once the molecule is converted back to testosterone, it is able to bind to a receptor and is an active steroid. Esters, as mentioned earlier, are usually attached at C-17, although they are sometimes found at C3. Generally, the shorter the ester chain, the shorter the half-life and quicker the drug enters circulation. Longer/larger esters usually have a longer half-life and are released into the circulation more slowly. Once in the circulation, the ester is cleaved, leaving free testosterone. Common testosterone preparations include testosterone propionate, testosterone cypionate, and testosterone enanthate.

In testosterone cypionate, the hydrogen from the hydroxyl group on C-17 has been removed and replaced with an 8-carbon side chain containing 1 cyclopentane ring and 1 carbonyl (=O) group. This is one of the larger esters of testosterone. In order of size, from smallest molecular weight to largest, the esters of testosterone are acetate, propionate, phenylpropionate, isocaproate, caproate, enanthate, cypionate, decanoate, undecylenate, undecanoate, and laurate. The largest of these esters, laurate, contains 12 carbon atoms, 24 hydrogen atoms, and 2 oxygen atoms. These esters can be attached to other steroids as well and are not limited to testosterone.

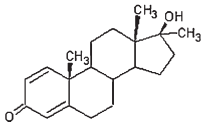
Common Testosterone Derivatives. The development of androgens was apparently centered on the need for drugs that exhibited characteristics different from those of testosterone. In general, the goal was to develop drugs that were more anabolic and less androgenic than testosterone, capable of being administered orally, and had less effect on the hypothalamic-pituitary-gonadal axis. Most androgens are derived from 3 compounds: testosterone, DHT, and 19-nortestosterone. The latter compound is structurally identical to testosterone except for the deletion of the 19th carbon, thereby resulting in its name. These parent compounds offer different properties with regard to action and metabolism that are generally constant throughout the entire family of compounds.

Methyltestosterone. Methyltestosterone (Metesto, Android) is a very basic androgen with the only addition being a methyl group at C-17. This eliminates first-pass degradation in the liver, making oral dosing possible. It also causes dose-related hepatotoxicity. It is metabolized by aromatase to the estrogen, 17-alpha methyl estradiol, and is also reduced by 5-α

TABLE 2. Types of anabolic steroids; structure and chemical properties.

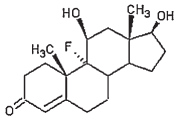
Name of Androgen	Chemical structure	Properties
Testosterone esters		
Testosterone cypionate		17-β-hydroxy-4-androsten-3-one Testosterone base + cypionate ester Formula: $C_{27}H_{40}O_3$ Molecular weight: 412.6112 Molecular weight (base): 288.429 Molecular Weight (ester): 132.1184 Formula (base): $C_{19}H_{28}O_2$ Formula (ester): $C_8H_{14}O_2$ Melting point (base): 155 Melting point (ester): 98–104°C Effective dose (men): 300–2000 mg+ week Effective dose (women): not recommended Active life: 15–16 d Detection time: 3 m Anabolic to androgenic ratio: 100:100
Testosterone enanthate (Primoteston)		17-β-hydroxy-4-androsten-3-one Testosterone base + enanthate ester Molecular weight: 412.6112 Molecular weight (base): 288.429 Molecular weight (ester): 130.1864 Formula (base): $C_{19}H_{28}O_2$ Formula (ester): $C_7H_{12}O$ Melting point (base): 155 Effective dose (men): 300–2000 mg+ week Effective dose (women): not recommended Active life: 15 d Detection time: 3 mo Anabolic to androgenic ratio: 100:100
Testosterone propionate		4-Androstene-3-one, 17beta-ol Testosterone base + propionate ester Molecular weight (base): 288.429 Molecular weight (ester): 74.0792 Formula (base): $C_{19}H_{28}O_2$ Formula (ester): $C_3H_6O_2$ Melting point (base): 155 Melting point (ester): 21°C Effective dose (men): 350–2,000 mg+ week Effective dose (women): 50–100 mg·wk^{-1} Active life: 2–3 days Detection time: 2–3 weeks Anabolic to androgenic ratio: 100:100
Common testosterone derivatives		
Methyltestosterone		[17alpha-methyl-4-androstene-3-one,17b-ol] Molecular weight: 302.4558 Formula: $C_{20}H_{30}O_2$ Melting point: 162–167°C Effective dose: 25–100 mg/·day^{-1}(men); not applicable in women Active life: 6–8 h Detection time: 4–6 wk Anabolic to androgenic ratio (range): 94–130:115–150

Methandrostenolone (Dianabol)



[17a-methyl-17b-hydroxy-1,4-androstadien-3-one]
Molecular weight: 300.44
Formula: $C_{20}H_{28}O_2$
Melting point: N/A
Effective dose: 25–50 mg (as low as 10 and as high as 100 have been reported)
Active life: 6–8 h
Detection time: up to 6 wk
Anabolic to androgenic ratio (range): 90–210:40–60

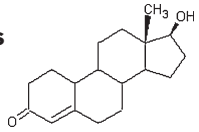
Fluoxymesterone (Halotestin)



[9-alpha-fluoro-11-beta-hydroxy-17-alpha-methyl-4-androstene-3-one,17b-ol]
Molecular weight: 336.4457
Formula: $C_{20}H_{29}FO_3$
Melting point: 240°C
Effective dose: 10–40 mg/d
Active life: 6–8 h
Detection time: 2 mo
Anabolic to androgenic ratio: 1,900:850

Common nandrolone derivatives

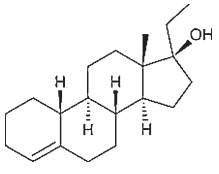
Nandrolone decanoate (Deca-Durabolin)



(Nandrolone base + decanoate ester)

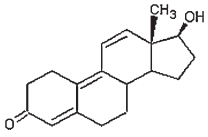
[19-nor-androst-4-en-3-one-17beta-ol]
Molecular weight (base): 274.4022
Molecular weight (ester): 172.2668
Formula (base): $C_{18}H_{26}O_2$
Formula (ester): $C_{10}H_{20}O_2$
Melting point (base): 122–124°C
Melting point (ester): 31–32°C
Effective dose (men): 200–600 mg·wk^{-1} (2mg·lb^{-1}of bodyweight)
Effective dose (women): 50–100 mg·w^{-1}
Active life: 15 d
Detection time: Up to 18 mo
Anabolic to androgenic ratio: 125:37

Ethylestrenol (Maxibolin, Orabolin)



[19-Nor-17alpha-pregn-4-en-17-ol]
Formula: $C_{20}H_{22}O$
Molecular weight: 288.46
Melting point: 76–78°C
Effective dose (men): 40 mg (?)
Effective dose (women): 10 mg (?)
Active life: 8–12 h

Trenbolone

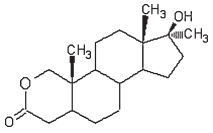


(17beta-hydroxyestra-4,9,11-trien-3-one)
(Trenbolone base + acetate ester)
Formula: $C_{20}H_{24}O_3$
Molecular weight: 312.4078
Molecular weight (base): 270.3706
Molecular weight (ester): 60.0524
Formula (base): $C_{18}H_{22}O_2$
Formula (ester): $C_2H_4O_2$
Melting point (base): 183–186°C
Melting point (ester): 16.6°C
Effective dose (men): 50–150 mg ED
Effective dose (women): not recommended
Active life: 2–3 d
Detection time: 5 mo
Anabolic to androgenic ratio: 500:500

(*Continued on next page*)

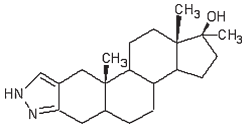
Common dihydrotestosterone derivatives

Oxandrolone (Anavar)



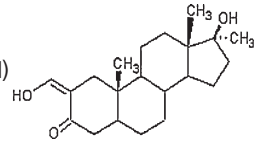
[17β-hydroxy-17a-methyl-2-oxa-5a-androstane-3-one]
Molecular weight: 306.4442
Formula: $C_{19}H_{30}O_3$
Melting point: 235–238°C
Effective dose–men: 20–100 mg·d^{-1} (or .125 mg·kg^{-1} body weight); women: 2.5–20 mg·d^{-1}
Active life: 8–12 h
Detection time: 3 wk
Anabolic to androgenic ratio (range): 322–630:24

Stanozolol (Winstrol)



[17beta-Hydroxy-17-methyl-5alpha-androstano [3,2-c] pyrazole]
Molecular weight: 344.5392
Molecular formula: $C_{22}H_{36}N_2O$
Melting point: N/A
Effective dose (men): 50–100 mg·d^{-1}
Effective dose (women): 2.5–10 mg·d^{-1}
Active life: 8 h
Detection time: 3 wk (oral) to 9 wk (injectable)
Androgenic to anabolic ratio: 30:320

Oxymetholone (Anadrol)



[17 beta-hydroxy-2-hydroxymethylene-17 alpha-methyl-5 alpha-androstan-3-one]
Molecular formula: $C_{21}H_{32}O_3$
Melting point: 178–180°C
Effective dose: 100 mg (optimal)
Active life: <16 h
Detection time: up to 8 wk
Androgenic to anabolic ratio: 45:320
Molecular Formula: $C_{21}H_{32}O_3$

reductase to 17-alpha-methyl DHT. This compound appears to exhibit very strong androgenic and estrogenic side effects, and its use is generally avoided for these reasons.

Methandrostenolone. Methandrostenolone (Dianabol) has an added *cis*-1 to *cis*-2 double bond in an attempt to reduce both estrogenic and androgenic properties. However, it does undergo aromatization to the estrogen, 17-alpha methyl estradiol, but is reduced by 5-α reductase to α-dihydromethandrostenolone (475). This steroid was first commercially manufactured in 1958 by Ciba under the brand name Dianabol and quickly became the most used and abused steroid worldwide to date. This agent is very anabolic with a half-life of approximately 4 hours. The methyl group at C-17 makes this anabolic-androgenic steroid an oral preparation and potentially hepatotoxic. Both Ciba and generic firms in the U.S.A. discontinued methandrostenolone in the late 1980s, but more than 15 countries worldwide still produce it in generic form.

Fluoxymesterone. Fluoxymesterone (Halotestin) is a potent androgen that is a substrate for 5-α reductase for conversion to DHT metabolites. With the addition of a 9-fluoro group, it becomes an androgen with very little anabolic activity; however, an added 11-β hydroxyl group inhibits its aromatization. The C-17 methyl group makes oral administration possible but not without apparent hepatotoxicity. This drug does not appear to be favored in clinical practice due to its poor anabolic effects, yet athletes typically use it for its apparent androgenic nature and lack of peripheral aromatization.

Common Nandrolone Derivatives. Nandrolone Decanoate: Nandrolone decanoate (Deca-Durabolin) is 19-nortestosterone with the addition of a 10-carbon decanoate ester added to the 17-β hydroxyl group. This addition extends the half-life of the drug considerably. Nandrolone is apparently a potent anabolic drug with a relatively favorable safety profile at therapeutic dosages. It is reduced by 5-α reductase in target tissues to the less potent androgen, dihydronandrolone. Nandrolone appears to possess a low affinity for aromatization to estrogen (501). Nandrolone and its esters (decanoate and phenylpropionate) differ only in their half-lives due to the difference in ester properties. Nandrolone decanoate is an injectable preparation and lacks the hepatotoxic C-17 group. It is one of the most widely abused drugs due to its efficacy, safety profile, and worldwide manufacture.

Ethylestrenol. Ethylestrenol (Maxibolin, Orabolin) is an oral 19-nortestosterone derivative and was marketed in the U.S.A., but it has since been discontinued. It differs from

nandrolone by the addition of a 17-α-ethyl group to reduce first-pass metabolism as well as the deletion of the 3-keto group. This latter omission seems to reduce AR binding. This drug appears to possess very little anabolic or androgenic effect at therapeutic doses.

Trenbolone. Trenbolone is a derivative of nandrolone with several additions. First, the addition of a *cis*-9 to *cis*-10 double bond supposedly inhibits aromatization, and a *cis*-11 to *cis*-12 double bond is considered to greatly enhance AR binding. This drug appears to possess potent androgenic and anabolic characteristics. It is comparably more androgenic than nandrolone due to its lack of conversion to a weaker androgen by 5-α reductase. Trenbolone is a European drug with a very high abuse record. In the U.S.A., it is used in veterinary preparations as trenbolone acetate.

Common Dihydrotestosterone Derivatives. Oxandrolone: Oxandrolone (Anavar) is a derivative of DHT, and because it is C-17 methylated, it is an oral preparation. The second carbon substitution with oxygen is thought to increase the stability of the 3-keto group and greatly increase its anabolic component. This drug is considered to be very anabolic with little androgenic effect at therapeutic doses. 5-α reductase does not appear to reduce oxandrolone to a more potent androgen, and because it is a DHT derivative, it cannot be aromatized. Oxandrolone is one of a few agents to be routinely abused by female athletes due to its mild androgenic properties. Athletes such as weightlifters, boxers, and sprinters use oxandrolone seeking to increase strength without additional weight gain.

Stanozolol. Stanozolol (Winstrol) is a drug with supposed anabolic and androgenic characteristics due to the stability afforded by the 3,2 pyrazol group on the first cyclohexane ring, which apparently greatly enhances AR binding. This drug can be C-17 methylated, thus making it an oral preparation; however, it also can be prepared as an injectable without C-17 methylation. Stanozolol appears to be active in both androgen- and anabolic-sensitive tissues. It is a weaker androgen than DHT that appears to exert comparatively less androgenic effect. As a result, it does not appear to aromatize to estrogenic metabolites.

Oxymetholone. Oxymetholone (Anadrol) is an oral drug because it is C-17 methylated. The 3-keto stability added by the 2-hydroxymethylene group supposedly enhances the drug's anabolic properties. The action of this agent in androgen-sensitive tissues is much like that of DHT; therefore, it quite androgenic. Oxymetholone is the only anabolic-androgenic steroid to date to be considered a carcinogen (466). This drug does not appear to be susceptible to aromatization. However, it is thought to activate estrogen receptors via the 2-hydroxymethylene group, thereby exerting many estrogenic side effects. In addition, because of the drug's C-17 methylation, it is considered to be hepatotoxic.

Designer Androgens. Indeed, an emerging clandestine industry has allowed athletes to evade detection via the use of novel "designer androgens." Several test-evading designer androgens have been identified in the past 3 years including a compound known as desoxymethyltestosterone, also known as Madol, that was never marketed (445) and a novel chemical entity that was specifically synthesized to evade detection (tetrahydrogestrinone, THG) (105). Desoxymethyltestosterone possesses the characteristics of a selective androgen receptor modulator (SARM) and displays potent anabolic effects (147). Tetrahydrogestrinone, implicated in the Bay Area Laboratory Cooperative (BALCO) investigation, was never marketed and apparently developed as a potent androgen that was undetectable by conventional International Olympic Committee (IOC)–mandated urinary sports doping tests. Tetrahydrogestrinone is a potent androgen and progestin that binds with high, but unselective, affinity to the AR and is able to transactivate AR-dependent reporter gene expression. However, this level of expression is 2 orders of magnitude lower compared with DHT (195).

Relative to designer androgens, their distribution for use at high doses without any prior biological or toxicological evaluation poses significant health risks. Although this diversion of science may highlight the possibility of tissue-specific effects highlighting the beneficial effects of androgens, the potential for undesirable effects may go unnoticed. As such, further developments require better understanding of the post-receptor tissue selectivity of designer androgens, comparable to the mechanism underlying that of selective estrogen receptor modulators (SERMs).

Selective Androgen Receptor Modulators. Testosterone and their synthetic derivatives, which are known to produce significant side effects (discussed in more detail later), spurred the development of SARMs. These synthetic ligands were designed to produce selective tissue-specific anabolic actions in muscle and bone, with minimal androgenic actions in other peripheral tissues. Selective androgen receptor modulators were first reported in 1998, and currently, several classes of SARMs exist including quinolines, tricyclics, bridged tricyclics, bicyclics, aryl propionamides, and tetrahydroquinolines (381,442). These ligands bind to the AR with high affinity, thereby strengthening the anabolic properties, yet are not subject to aromatase or 5α-reductase activity so their androgenic properties are low (381,442). In addition, they have favorable pharmacokinetic properties and great potential for biochemical modifications indicative of a more favorable alternative to anabolic steroids and related compounds for therapeutic interventions (442).

History of Androgen Use

The interest in improving physical performance appears to have occurred as an offshoot of early research, which sought to determine the physiological and performance effects of testicular extracts (194). As early as 1849, scientists had

suggested that a substance secreted by the testes into the blood stream was related to physiological and behavioral characteristics of male animals (194). In 1889, Brown-Séquard, considered by many as one of the founding fathers of modern endocrinology, published results from his auto-experimentations on testicular substances in which he reported increases in muscular strength, mental abilities, and appetite (156,194). Although the results of his work were never substantiated, it did give rise to the new field of organotherapy in which testicular extracts were injected or testicles were transplanted into patients with various disorders (194). By the end of 1889, some 12,000 physicians were administering Brown- Séquard's testicular extracts as the new "elixir of life" (227,494).

Largely based on Brown-Séquard's work, Zoth and Pregl began to investigate the effects of injections of testicular extracts on muscle strength and athletic performance (156,244). Zoth and Pregl injected themselves with extracts from bull testicles and measured strength of their middle fingers and recorded fatigue curves during a series of exercises. In 1896, Zoth published an article suggesting that injections of testicular extracts improved muscular strength and the "neuromuscular apparatus" (156,244). Although it is likely that these results were placebo effects, Zoth may be the first person to suggest injecting athletes with hormones in an attempt to increase performance (243,244).

Not until 1929 was the first sex hormone isolated (156,243,244). In 1929, Butenandt was the first to isolate the sex hormone estrone from the urine of pregnant women and later was credited with isolating 15 mg of androsterone ("andro" = male, "ster" = sterol, "one" = ketone) from the urine of local policemen (156). Ultimately, comparisons were made between sex hormones isolated from urine and those isolated from the testes. These comparisons revealed that the hormones isolated from the testes had greater androgenic properties than those extracted from the urine (244). Once sex hormones were isolated, a new path of scientific discovery was initiated.

In the 1930s, pharmaceutical companies were very interested in isolating the testicular hormone, which in 1935 was termed testosterone ("testo" = testes, "ster" = sterol, "one"= ketone) by Kàroly David and his research team (130,156). During the 1930s, there was a great interest in synthesizing artificial testosterone, and in 1935, Butenandt and Hanish published the first paper documenting the synthesis of testosterone from cholesterol (130,156). Only 1 week later Ruzicja and Wettstein also published a paper that outlined another method for the synthesis of artificial testosterone (429). Around this time, Kochakin reported that androgens could stimulate protein anabolism and stimulate growth. It was further speculated that androgen therapies may be effective in stimulating growth and restoring tissue in subjects with a variety of disorders (156,245). Shortly after its synthesis, oral and injectable testosterone preparations became available to the medical community (544).

Much of the early research looking at human use of testosterone was conducted in Germany before World War II (500). In fact, some have speculated that German athletes may have been given testosterone in preparation for the 1936 Olympics (544). Additionally, it has been suggested that German soldiers were given testosterone to increase aggressiveness in battle during this time frame (519). However, to date, no data have been discovered to substantiate the use of testosterone by either German athletes or soldiers during this period (544).

Clinical trials designed to explore the effect of exogenous testosterone use on humans were underway as early as 1937 (244). This early work involved the injection of testosterone propionate and the oral consumption of methyltestosterone (156,244). Ultimately, the early testosterone studies explored the effects of the newly synthesized compound as a tool for treating men with hypogonadism and impotency (244). At this time, testosterone therapies were also used to treat a variety of medical conditions associated with women including menorrhagia, painful breast syndrome, dysmenorrhea, and estrogen-driven breast cancers (244). The administration of testosterone in women during this period revealed that the daily use of topical testosterone preparations resulted in increased sexual desires and clitoral hypertrophy (243,244). Although the administration of testosterone to women consistently resulted in an increased sex drive, it did not become a standard therapy because of the noted side effects associated with the drug. Clinicians in this period noted that women who were treated with testosterone preparations not only experienced clitoral hypertrophy but also experienced increased hair growth on the body and face and demonstrated a deep husky voice (243,244). The occurrence of these side effects resulted in many heated debates in the scientific literature about the efficacy of using testosterone therapies in women (244).

In 1939, Bjoe suggested that sex hormones might enhance physical performance (71). During the 1940s, it was discovered that testosterone could facilitate muscular growth and much speculation about the performance effects of testosterone occurred (244). This hypothesis was confirmed in 1942 when Kearns and colleagues (286) reported that the implantation of a testosterone pellet in a gelding coupled with training significantly improved physical performance. It was also speculated that the age-induced declines in working capacity were directly related to the concomitant declines in testosterone seen with aging. This led to further speculation that testosterone therapies may be able to increase working capacity as one ages (243,244).

de Kruif in his popular text "The Male Hormone" raised the hopes and expectations for the use of testosterone by suggesting that the administration of testosterone could increase muscle mass, rejuvenate individuals, and elevate their working capacity (135). In fact, de Kruif suggests that it would be interesting to see what athletes who were systematically using testosterone could do in competition (500). Several

reports suggest that West Coast bodybuilders in the late 1940s and early 1950s began experimenting with the use of testosterone preparations (244,544). Additionally, it appears that the use of testosterone and its synthetic derivatives began to infiltrate sports during the 1950s (500,544).

At the 1952 Olympic Games, the Soviet Union did exceptionally well in the weightlifting competition, which led to speculation that some sort of hormone manipulation was being employed (500). This contention seems to be supported by statistical analyses of the performance of the Soviet weightlifters during this time frame (176). In 1954 at the World Weightlifting Championships, Dr. John Ziegler was told by his Soviet counterpart that the Soviet weightlifters were indeed using testosterone (500). After the completion of the world championships, Dr. Zeigler returned to the U.S.A. and immediately began experimenting with testosterone use. In his early work with testosterone he became concerned with potential side effects, such as prostate problems and increased libido (500). Ultimately, this led him to search for a drug that had pronounced anabolic effects while minimizing the androgenic effects (500).

In 1958, the first U.S. manufactured androgen Dianabol (methandrostenalone) was approved by the U.S. Food and Drug Administration (156,500). This new drug provided a potential solution to the side effects noted with testosterone use. To explore the effectiveness of Dianabol administration in athletes, Dr. Ziegler administered the drug to 3 members of the York Barbell Weightlifting team (500). Dianabol proved to be a very effective drug when coupled with resistance training, and the athletes experienced a meteoric rise in performance (500). News of the drug's application as an ergogenic aid spread to other strength- and power-based sports including the field events in track and field and American football (544).

In 1960, the use of androgens by Olympic athletes was still not a major problem and was probably limited to American and Soviet strength athletes (544). By the 1964 Olympic Games, the use of androgens became significantly more extensive in all strength sports (500,544) and was a growing problem (98). In 1965, oral turinabol was synthesized by a German Democratic Republic (GDR) state–owned pharmaceutical company (505). By 1966, the GDR began a state-sponsored doping program designed to enhance sports performance and prepare athletes for the 1968 Olympic Games in Mexico City (191). Interestingly, it appears that the GDR was the first to administer the drug to women athletes as they prepared for the 1968 Olympic Games (191,505)

With the increasing use of performance-enhancing drugs and several high-profile deaths of athletes from various sports, the IOC established a medical commission in 1967. The primary goal of the IOC Medical commission was to develop a list of prohibited substances and methods (192). The IOC also adopted a medical code that encompassed 3 principles: (a) protection of the health of the athlete, (b) respect for both medical and sports ethics, and (c) equality for all competing athletes (192).

By the 1968 Olympics, an incremental increase in use was seen in track and field (544). Support for this contention can be seen in reports that suggest that one-third of the U.S. track and field team (i.e., throwers, sprinters, hurdlers, and middle distance runners) had used these drugs in the lead up to the 1968 Olympic Games (500). Additionally, documentation has been discovered that reveals that at the 1968 Olympics many of the male and female athletes from the GDR were systematically using various anabolic-androgenic drugs to enhance athletic performance (191). Although androgen use was on the rise during this time frame, there was little debate about the ethics of taking androgens. Most discussion among athletes centered on which drugs were most effective (544).

In 1969, androgen use was so prevalent that John Hendershott the editor of *Track & Field News* called these drugs the "breakfast of champions" (234). Throughout the 1960s, the overall volume of androgen use increased dramatically. In fact, it appears that athletes increased the dosages used to levels that were 2–5 times above the recommended therapeutic dosage (544) and performance gains increased (191). Additionally, athletes began preferentially taking androgens and began experimenting with stacking drugs that included a combination of oral and injectable forms (544). During these years, the IOC failed to include androgens on the banned substance list. One reason for this was that the medical community suggested that androgens were ineffective and were unwilling to consider that the use of these drugs could impact performance. This was primarily based on several poorly designed studies (this will be discussed in greater detail in the next section). Ultimately, this caused a large credibility gap between athletes and the medical community as many athletes developed a large distrust for medical doctors (500). The second reason for the exclusion of androgens was that there simply were no reliable and valid tests at this time (500).

In 1973, the first testing procedures for androgens were proposed. The first method used radioimmunoassay procedures, whereas the second suggested using a combination of gas chromatography and mass spectrometry (GC-MS) techniques. The IOC ultimately adopted both methods to ensure the highest accuracy in testing; however, very few laboratories in the world could conduct the test at the levels required by the IOC. The testing protocols were first implemented in the 1974 Commonwealth Games in Auckland, New Zealand, where 9 out of 55 samples were positive for androgens (500).

Throughout the early 1970s, the GDR expanded its doping program to include most sports, and it became customary to provide drugs to most athletes including minors (191). In fact, the overall dosages of the drugs used by athletes from the GDR continued to escalate to the point at which damaging side effects became apparent, especially in the female athletes who were outwardly androgenized (191). With the advent of

testing in 1974, the GDR faced a very unique problem in that it was apparent that the use of androgens was a key to their success in international competition, but the advent of drug testing created a possible problem to the systematic program being used. At the 1974 European Athletic Championships in Rome, drug testing of urine samples revealed no positive steroid tests. However, the IOC was developing new drug testing processes that created a situation in which the GDR feared many of its most successful athletes would test positive (191).

In 1974, the GDR government instituted a top secret program that provided for the administration of androgens and other doping products to male and female athletes. This program contained 6 central concepts, which included (a) the mandate that doping plays a central role in the training process and preparation of athletes for major international competition; (b) the establishment of a monitoring program in which sports physicians conducted regular evaluations of the athletes; (c) the development of a centralized drug distribution and documentation program, which was under the control of the Sportmesizinischer Dienst (SMD); (d) the organization of a systematic research program into the development of new doping products and the establishment of drug administration programs, which would allow for the avoidance of detection during doping controls; (e) the development of a comprehensive educational program in which coaches and physicians would be instructed about doping; and (f) the classification of the doping program as an Official State Secret (191). The timing of the program was extremely important as the IOC had planned to test at the 1976 Olympic Games and the GDR wanted to continue to build upon its growing success in international competitions.

In 1976, drug testing was first initiated at the Olympic Games in Montreal (500). A relatively low number of athletes tested positive for androgens during these games (8 out of 275 tests) (500). Although it appeared few athletes were doping based on the drug testing program instituted by the IOC, survey data collected during the games suggested that as many as 68% of the athletes competing had used androgens during their training (98). It is likely that the early drug testing programs were not as effective due to the fact that the IOC had left off many drugs from their testing program (500). For example, norbolethone, which was never approved for human consumption, was reported to be taken by several athletes but was not present on the early lists of banned substances (98). Additionally, it has been reported that many athletes reverted to the use of testosterone, as it was not part of the original testing program (500).

By 1979, the GDR doping program had expanded to the point that athletes were being given complex combinations of drugs. For example, Franke and Berendonk (191) reported that one GDR weightlifter was administered 11.55 g of oral turinabol, 13 injections of testosterone esters, and human chorionic gonadotropin (hCG). Most noted was the development of "steroid bridging," which replaced readily detectable steroids with testosterone esters in the weeks before competition to circumvent drug testing protocols. Typically, athletes would receive repeated intramuscular injections of testosterone esters of various fatty acid chain lengths in the time period leading up to a major competition (191). This process was quite commonplace in the GDR and many other countries. Before the 1980s, there was no method available for the detection of testosterone use to drug testers.

In 1980, Professor Manfred Donike the head of the IOC-approved drug testing laboratory in Cologne, West Germany, developed a method for detecting testosterone use by comparing the testosterone to epitestosterone ratio (T:E ratio) (500). Because the use of testosterone results in an increase in testosterone levels without a concomitant increase in epitestosterone, athletes who possessed a T:E ratio of 6:1 were suggested to be doping. After the 1980 Olympic Games in Moscow, the T:E ratio was determined and it was detected that ~20% of all athletes tested had a T:E ratio of >6:1 (29) and 7.1% of female athletes tested had a T:E ratio of >6:1 (191). After the development of the T:E ratio test, the IOC implemented the protocol as part of its doping controls.

The advent of the T:E ratio test caused significant problems for the state-instituted doping program of the GDR. In a 1981 meeting in the GDR, it was determined that a program to find alternatives to exogenous testosterone administration was needed and that testosterone was to be replaced by its precursors (i.e., androstenedione, DHT, dihydroanodrostenedione, or DHEA) (191). By 1982, scientists from the GDR had determined that 3 days after the injection of 25 mg of testosterone propionate, the T:E ratio would be below the 6:1 cutoff used by drug testers. Additionally, it was discovered that hCG and clomiphene did not alter the T:E ratio (191). By 1983, the GDR had determined a method for simultaneously injecting testosterone and epitestosterone, which consistently kept the T:E ratio below the 6:1 cutoff. With this information in hand, the GDR had a method that allowed them to circumvent doping controls.

The T:E ratio test was first administered at the 1983 Pan American Games in Caracas, Venezuela, where a total of 15 athletes tested positive (11 weightlifters, 1 cyclist, 1 fencer, 1 sprinter, and 1 shot putter) (500). There may have been more positive tests but 12 American athletes chose to leave the games before competing and thus avoided being tested. Journalists and commentators seemed shocked by the apparent doping problems that were brought to light by the Pan American Games in Caracas (500). At this time, journalists began reporting that androgens were not only a part of Olympic sports such as weightlifting but were also a part of every other professional sport in America. More disturbing was the fact that collegiate (e.g., National Collegiate Athletic Association [NCAA]) and professional sport (e.g., NFL, MLB, NBA, and NHL) organizations, and even professional bodybuilding, were doing nothing to curb the use of androgens (500). For example, it has been speculated that between 50 and 75% of offensive and defensive

linemen in the NFL used steroids during the 1980s, but the precise level of use will probably never be known (544).

Although the T:E ratio test was implemented at the 1984 Olympic Games in Los Angeles, the most famous androgen positive occurred at the 1988 Seoul Olympic Games when Canadian sprinter and then current world's fastest man Ben Johnson tested positive for stanozonol (98). This positive test sent shock waves through the sporting community, ultimately resulting in the U.S. government passing the Anti-Drug Abuse Act, which made it illegal to distribute or possess androgens (98). Additionally, the IOC expanded the banned substance list to include diuretics, such as probenecid, and other products typically used to mask androgens use (315). In 1990, the U.S. government went a step farther when it passed the first Anabolic Steroid Control Act and inserted 27 steroids, along with their muscle building salts, esters, and isomers as class III drugs and simple possession could result in prison time (117)

As drug testing became more developed, the interest in the use of dietary supplements as performance enhancement tools increased. In 1994, the U.S. government passed the Dietary Supplement Health and Education Act (DSHEA), which was designed to protect the consumer from the risks of taking certain substances. For example, the Food and Drug Administration used this act to ban ephedra (117). In 1996, the prohormone androstenedione, which was first used by the GDR in 1981, was introduced to the American market as a new dietary ingredient (117). Because it was classified as a new dietary ingredient, it was not subject to regulation by the DSHEA (117). In fact, androstenedione became a very popular dietary supplement when Mark McGwire admitted to using it in 1998 (116).

In 1999, the IOC took an unprecedented step and convened the World Conference on Doping in Sport in Lausanne, Switzerland. Ultimately, this conference served as the foundation for the formation of an international anti-doping initiative, which resulted in the formation of the World Anti-Doping Agency (WADA) in 2001 (192). By 2002, WADA had developed the world anti-doping code, which contained 3 major parts: (a) the code, (b) international standards, and (c) models of best practice (192). The international standards serve as the operational and technical areas that are contained within the anti-doping program and integrate anti-doping agencies with the overall anti-doping code. The anti-doping code contains international standards for (a) laboratories, (b) testing procedures, (c) substances contained on prohibited lists, and (d) mechanisms and rules for therapeutic exemptions (192). As a whole, WADA oversees doping controls for international competitions including the Olympic Games and world championships as well as other sporting events that fall under the IOC (192). These doping controls are not only performed at competitions but are also performed as no-notice out-of-competition controls. In this capacity, WADA requires athletes to report their whereabouts so that random drug testing can be conducted. If the athlete either fails a doping control test or fails to show for testing WADA has the power to sanction athletes, which ultimately can withhold them from competition indefinitely depending upon the number of doping offenses the athlete has. Since 2000, WADA has performed out-of-competition testing for sports, which are encompassed under the IOC governance. However, to date, professional sports in America have yet to allow WADA to perform in or out-of-competition testing in their sports, and it is unlikely that they ever will.

In 2003, a syringe containing an unknown compound was sent to the U.S. Anti-Doping Agency that would expose a doping program that could only be compared with the program once run by the GDR (105,296). Eventually, the compound in the syringe was isolated and determined to be THG, which was at the time a new undetectable steroid (105,296,298). After its isolation, the drug source was linked to the BALCO, and the subsequent scandal associated with this drug exposed a widespread doping problem in American sports (298). By 2004, a second designer steroid known as Madol was isolated by the UCLA laboratory (445). The discovery of these designer steroid compounds suggests that unscrupulous athletes and scientists are still trying to circumvent the drug testing controls, much like the GDR did in the 1980s.

In 2004, the U.S. Senate held hearings on the abuse of androgens and their precursors by athletes. By the end of 2004, a new Anabolic Steroid Control act was implemented, which contained 26 new steroid compounds, including many of the steroid precursors such as androstenedione and androstenediol. Additionally, designer steroids such as THG were also added to the controlled substances listed by the act (117).

Another change in the world of doping controls occurred in 2005 when WADA lowered the T:E ratio, which indicated an adverse analytical finding from 6:1 to 4:1 (536). If the athlete were to test positive for an elevated T:E ratio (>4:1), then a follow-up test consisting of the use of an isotope ratio mass spectrometry (IRMS) procedure was to be used (536). Ultimately, the IRMS test was suggested to be an accurate way to determine if synthetic doping products were taken by the athlete (1). The advent of these new testing procedures would result in some interesting doping findings in 2006 (further discussion on testing for androgens will be presented later in this report).

In 2006, the sporting world was yet again rocked by another doping scandal. Before the 2006 Tour de France, the Spanish Civil Guard began investigating Dr. Eufemiano Fuentes for providing doping products to cyclists and athletes from other sports (328). The investigation resulted in several high-level cyclists being excluded from the Tour de France in 2006 and some were subsequently sanctioned. At the end of the 2006 Tour de France, it was revealed that the winner American Floyd Landis tested positive for an abnormal T:E ratio and as of 2008 he has been stripped of his title under the suspicion of using testosterone (168). Up to this point, it was widely

believed that androgens use was limited to strength and power athletes. However, evidence from this race revealed that androgen use was now prevalent in endurance-based sports as well.

In 2007, Marion Jones admitted to taking banned drugs including THG during the 2000 Olympic Games in Sydney, Australia (410). What is unique about the Marion Jones case is that she was proven guilty of doping without ever testing positive for performance-enhancing substances. She was initially linked to the BALCO scandal in 2004 and repeatedly denied using anabolic steroids, but in 2007, she admitted to using performance-enhancing drugs before and during the 2000 Olympic Games. By the end of 2007, an independent report on androgen use in professional baseball was released, which suggested that the use of androgens and other performance-enhancing drugs is a serious problem in professional baseball in the U.S.A. (360). Table 3 provides a time line of the history of androgen use.

Research on Androgens as a Performance-Enhancing Drug

Studies investigating the performance-enhancing effects of androgen administration have yielded conflicting findings. Although athletes were making significant gains with androgen use since the mid-1950s (with a possibility athletes may have began to experiment with androgens prior to this period of time), early research did not corroborate the anabolic and ergogenic effects experienced by athletes. Thus, academia decried their efficacy citing a lack of evidence. In fact, the ACSM between 1976 and 1984 regarded androgens as being ineffective until they revised their position in 1984 (9,10). Several important factors must be considered when interpreting results of these studies. For example, some early studies that have shown limited effects were plagued by poor scientific design (i.e., nonrandomized, not double-blind, no-placebo trials used) and issues that contrasted with how athletes were using androgens in real-world settings. In these studies, researchers oftentimes administered too low a dose of androgens (e.g., a clinical dose or lower typically prescribed for androgen deficiency, which is far exceeded by athletes), and this study did not have subjects train in conjunction with androgen use (e.g., whereas athletes were training at a high level), did not examine "stacking" of androgens or the compounding effects of multiple-drug use (e.g., most androgen users stack multiple drugs), used untrained subjects (which undergo an extend neural phases initially that may mask potential increases from androgens), and failed to examine dietary interventions such as increased protein intake coinciding with androgen use (e.g., many androgen users increase protein and kilocalories consumption greatly). This information notwithstanding, androgen research before 1980 was inconsistent regarding its efficacy.

Androgen Studies Before 1980. An early performance study was performed by Samuels and colleagues (434) who reported that 50 $mg \cdot d^{-1}$ of methyltestosterone (plus 250 mg of creatine hydrate) for 3 weeks did not enhance grip strength in untrained subjects. Nearly a quarter of a century had passed before androgen ergogenicity studies resurfaced with greater frequency predominantly in non–resistance-trained subjects. Several studies did not report ergogenic effects of anabolic steroids on muscle strength or performance. Fowler et al. (190) administered 20 $mg \cdot d^{-1}$ of methenolone acetate (Nibal) for 16 weeks to untrained subjects who either did not exercise or exercised 30 $min \cdot d^{-1}$, 5 $d \cdot wk^{-1}$ and reported that androgen use did not enhance muscle size, body weight, or isometric strength. Weiss and Muller (527) also did not report any greater enhancement of grip strength or body weight after administration of 10 mg of Dianabol for 17 days in high school students. Casner et al. (104) administered 6 $mg \cdot d^{-1}$ of Winstrol in some subjects' weight training 3 $d \cdot wk^{-1}$ and reported no ergogenic effects of androgens on isometric strength, although body weight gains were greater in the androgen/lifting group. Fahey and Brown (174) administered 1 $mg \cdot kg^{-1}$ body mass of Deca-Durabolin every second or third week for 9 weeks in college students' weight training 3 $d \cdot wk^{-1}$ (3–5 sets of 1–5 repetitions) and reported statistically similar increases in strength compared with a control group (13–15 kg compared with 6–10 kg). Stromme et al. (486) administered 75 $mg \cdot d^{-1}$ of mesterolone (Mestoranum) for 4 weeks and 150 $mg \cdot d^{-1}$ for the subsequent 4-week period in college students taking a weight training class and reported similar increases in isometric strength to a control group. Hervey and colleagues (237,238) administered 100 mg of Dianabol (or placebo) for 6 weeks in a crossover design and reported greater gains in body weight and girth measurements with androgen use, but no significant difference was observed in lifting performance between androgen and placebo conditions. Loughton and Ruhling (329) administered 10 $mg \cdot d^{-1}$ of Dianabol for 3 weeks and 5 $mg \cdot d^{-1}$ for 3 more weeks concomitant with weight training and running program and reported greater weight gains in the androgen group but nonsignificant interactions in strength performance.

Several early studies in lesser trained individuals did show ergogenic potential of androgens. Johnson and O'Shea (273) weight trained subjects for 6 weeks but administered 10 mg of Dianabol (plus protein) daily the last 3 weeks to half of the subjects and reported significantly greater gains in isometric strength and 1 repetition maximum (1RM) squat (although other strength measures did not reach statistical significance) in the steroid group. In a follow-up study, Johnson et al. (272) reported similar findings where androgens enhanced muscle strength and girth to a greater extent. Win-May and Mya-Tu (533) administered 5 $mg \cdot d^{-1}$ of Dianabol to university students over 3 months (little was known about their physical activity) and reported greater gains in grip strength, push-up, and pull-up performance in the steroid group.

Most early studies examining androgen use in trained subjects demonstrated ergogenic potential in muscular strength and performance. O'Shea and Winkler (379) administered 10 $mg \cdot d^{-1}$ of Anavar (plus protein) to swimmers and weightlifters for 6 weeks and reported large

TABLE 3. Time line of major events related to androgen use.*

Year	Author	
1889	Brown-Séquard	Presents data on autoexperimentation of the injection of testicular extracts. Suggests improvements in muscular strength occur.
1896	Zoth and Pregl	Investigated the effects of testicular extracts on muscle strength and athletic performance and were the first individuals to suggest injecting athletes with hormones.
1928		The International Amateur Athletics Federation (IAAF) becomes the first sports federation to ban the use of doping products (i.e., stimulants)
1929	Butenandt	Isolated the esterone from the urine of pregnant women and later androsterone from urine of local policemen.
1935	David et al.	Isolated the testicular hormone known as testosterone.
1935	Butenandt and Hanish	Published first paper on the synthesis of testosterone from cholesterol.
1935	Ruzicja and Wettstein	Published second paper on the synthesis of testosterone.
1935	Kochakin	Reported testosterone stimulates protein anabolism and stimulates growth. Suggested that testosterone therapies may be useful for several disorders.
1937		Clinical trials looking at testosterone conducted.
1938		Androstenedione synthesized.
1939		Testosterone administered to women for a variety of medical conditions is begun. Noted effects are increases in sex drive and clitoral hypertrophy. Side effects such as a deeper voice and the increase growth of facial and body hair are also noted.
1939	Boje	Suggests sex hormones may enhance physical performance.
1942	Kearns et al.	Report that administration of testosterone improved performance of a gelding trotter.
1944		Speculation that reductions in work capacity with age are related to age-induced declines in testosterone.
1945	de Kruif	Published the book *The Male Hormone* in which he touts the use of testosterone for increasing muscle mass and increasing work capacity. Suggests it would be interesting to see what athletes who were systematically using testosterone could do in competition.
1952	Hoffman	Bob Hoffman of York Barbell speculates that the Soviets have used hormones to elevate performance during the Olympic Games.
1954	Zeigler	Zeigler told by Soviet team physician that Soviet Weightlifters were using testosterone.
1958		Ciba Pharmaceutical Company releases Dianabol
1959	Zeigler	Once dianabol (methandrostenolone) was synthesized began testing it on members of the York Barbell Weightlifting Team.
1960		Speculation that anabolic-androgenic steroid use is limited to Soviet and American weightlifters
1960		Death of a Danish cyclist at the 1960 Olympics puts pressure on sports authorities to deter doping (amphetamine use)
1962		The Council of Europe published an initial list of banned substances including narcotics, amine stimulants, alkaloids, respiratory tonics, and certain hormones.
1964		Anabolic-androgenic steroid use increases to include most strength power athletes.
1965		Oral turinabol was synthesized by VEB Jenapharm, a German Democratic Republic State owned pharmaceutical company.
1966		The German Democratic Republic begins a systematic program to investigate and administer illegal drugs including anabolic-androgenic steroid to athletes. First documented systematic program to administer anabolic-androgenic steroids to women.
1967		British cyclist died during the Tour de France as a result of amphetamine use.
1967		International Olympic Committee establishes a medical commission and banned drugs.
1967		International Olympic Committee adopts a medical code which encompassed 3 principles: (a) protection of the health of the athlete, (b) respect for both medical and sports ethics, and (c) equality for all competing athletes.

(*Continued on next page*)

1968		Anabolic-androgenic steroid use increases. Estimated that one-third of the U.S. track and field team used the drug in the 1968 Olympics. Most athletes from the German Democratic Republic were systematically using anabolic-androgenic steroids.
1968		Drug testing was conducted for research purposes at the 1968 Winter Olympic Games in Gernoble, France, and the Olympic Summer Games in Mexico City, Mexico. Anabolic-androgenic steroids were not tested for, as they were not banned at this time.
1969	Hendershott	The editor of *Track & Field News* called anabolic-androgenic steroids the breakfast of champions.
1973		Radioimmunoassay and a combination of gas chromatography and mass spectrometry suggested as possible test for anabolic-androgenic steroids. To ensure accuracy, both testing procedures were adopted by the International Olympic Committee.
1974		First anabolic-androgenic steroid testing conducted at the Commonwealth Games in Auckland, New Zealand. No sanctions were administered, despite 9 of 55 samples contained anabolic-androgenic steroids.
1974		The German Democratic Republic institutes a Top Secret program to systematically dope athletes and circumvent IOC instituted drug testing
1975		First sanctions for positive anabolic-androgenic steroid drug test handed out to 2 track athletes competing at the European Cup.
1976		Drug testing was instituted at the 1976 Olympic Games. Eight athletes out of 275 tested were found to be positive for anabolic-androgenic steroids (7 weightlifters and 1 discus thrower). Two of the weightlifters were Americans, Mark Cameron and Phil Grippaldi.
1980		Dr. Donike developed test for testosterone, 6:1 testosterone to epitestosterone ratio established as a screening tool for doping.
1980		Testing of unused urine samples from the 1980 Moscow Olympic Games revealed that 20% of all athletes had T:E ratios greater than 6:1 and 7.1% of all female athlete samples were above the 6:1 ratio.
1981		GDR decided to replace testosterone administration with androstenedione, various forms of dihydrotestosterone, dihydroandrostenedion, or dehydroepiandrosterone
1982		Testing for testosterone was introduced for the 1984 Olympic Games by the IOC, the T:E ratio is set at $>$6:1.
1982		GDR begins the administration of hCG, Clomiphen that did not affect T:E ratio. Additionally, the GDR discovers that 3 days after the injection of testosterone propionate, the T:E ratio was below 6:1.
1983		The GDR discovers the dosage of epitestosterone needed to keep the T:E ratio below 6:1 when exogenous testosterone was used.
1983		Testosterone screening is first conducted at the 1983 Pan American Games in Caracas Venezuela. Fifteen athletes were caught for doping: 11 weightlifters (some were using testosterone), 1 cyclist, 1 fencer, 1 sprinter, and 1 shot putter.
1984		First use of the T:E ratio test at the Olympic Games in Los Angeles.
1988		Ben Johnson tested positive for Stanozolol at the 1988 Olympic Games
1988		Testing for diuretics and other masking agents for anabolic-androgenic steroids begins.
1988		The U.S. government passed the Anti-Drug Abuse Act, making the distribution or possession of anabolic-androgenic steroids for nonmedical reasons a federal offense.
1990		The U.S. government passed the first Anabolic Steroid Control Act and inserted 27 steroids, along with their muscle building salts, esters, and isomers as class III drugs and simple possession could result in jail time.
1994		The U.S. Congress passed the Dietary Supplement Health and Education Act.
1996		Androstenedione was first marketed as a dietary supplement in the U.S.A.
1998		Mark McGwire admitted using androstenedione; consequently, sales of the dietary supplement increase incrementally.
1998		A large number of prohibited medical substances were found during drug raids conducted at the Tour de France.
1999		The first World Conference on Doping in Sport was held in Lausanne, Switzerland.
2001		The World Anti-Doping Agency was formed.
2001–2002		The world anti-doping code was developed by the World Anti-Doping Agency.

2002	The first known designer steroid Norbolethone was isolated by the UCLA Olympic Analytical Laboratory.
2002	American Track Cyclist Tammy Thomas banned for life for taking Norbolethone.
2003	Syringe sent to USADA with unknown substance. Later determined to be designer steroid known as tetrahydrogestrinone.
2003	Bay Area Laboratory Cooperative Scandal Revealed linking many athletes to doping
2004	The second known designer steroid Madol was isolated.
2004	U.S. Senate holds Hearing on Anabolic-Androgenic Steroids and their precursors by athletes.
2004	The Anabolic Steroid Control Act is revised to include 26 new compounds including many of the steroid precursors that to this point were commonly sold as dietary supplements.
2004	IOC opens investigation into Marion Jones who was linked to the BALCO scandal.
2005	T:E ratio for a positive doping test is lowered to 4:1 by WADA. A T:E ratio of >4:1 is indicated as an adverse analytical finding and isotope mass spectrometry is then used to determine the presence of synthetic testosterone.
2006	The Spanish Civil Guard investigated Dr. Eufemiano Fuentes for running a doping ring. The doping scandal linked to athletes in cycling and a variety of sports.
2006	Floyd Landis tested positive during the Tour de France for an abnormal T:E ratio.
2007	Marion Jones admitted to doping during the 2000 Olympic Games and was subsequently stripped of her medals and records.
2007	Mitchell Report on Steroid Use in Professional Baseball is released.

*GDA = German Democratic Republic; IOC = International Olympic Committee; USADA = U.S. Anti-Doping Agency; WADA = World Anti-Doping Agency.

improvements in strength, although no control group was used for comparison. O'Shea (377) administered 10 $mg \cdot d^{-1}$ of Dianabol for 4 weeks to weightlifters (half consumed anabolic steroids, half consumed a placebo) and reported greater strength gains in bench press in the steroid group (but 30% greater increase in squat strength in the steroid group was not significant). Bowers and Reardon (78) administered 10 $mg \cdot d^{-1}$ of Dianabol (plus 30 g of protein per day) to resistance-trained men for 3 weeks and reported greater strength increases in the steroid group. Ariel (20) administered 10 $mg \cdot d^{-1}$ of Dianabol for 4 weeks to resistance-trained varsity athletes and reported that rate of strength gains was greater with steroid use than with placebo. In 2 other studies, Ariel (21,22) administered 15 $mg \cdot d^{-1}$ of Dianabol for 4 weeks in a crossover design and reported greater strength gains with androgen use. Interestingly, subjects who consumed a placebo first made greater gains than subjects who consumed a placebo the last 4 weeks, indicating that strength gains were attenuated when androgens were discontinued. In the second study, Ariel (22) reported that strength gains from androgen use did not deteriorate as fast as gains made during placebo consumption in subjects following a protocol similar to that followed in the previous study over a subsequent 15-week period of detraining. Ward (524) administered 10 $mg \cdot d^{-1}$ of Dianabol (or placebo) for 4 weeks to weight-trained college men during training (3 $d \cdot wk^{-1}$, 4 sets of 5 repetitions) and reported significantly greater gains in bench press and squat strength in the androgen group than in group receiving placebo. Stamford and Moffatt (473) administered 20 $mg \cdot d^{-1}$ of Dianabol (plus 30 g of protein) for 4 weeks in resistance-trained men and reported accelerated strength gains in the androgen group compared with placebo. O'Shea (378) administered 8 $mg \cdot d^{-1}$ of Winstrol (plus 0.5 $g \cdot kg^{-1}$ of protein) to weight-trained men (1–2 years of experience) for 5 weeks and reported that only the androgen group increased maximal bench press and squat strength. Freed et al. (193) administered 10 or 25 $mg \cdot d^{-1}$ of Dianabol to trained lifters for 6 weeks and reported greater strength improvements in the androgen groups but no dose-response relationship was found. However, Golding et al. (207) administered 10 $mg \cdot d^{-1}$ of Dianabol (3 weeks on, 1 off) for 12 weeks to trained lifters and reported no significant greater strength gains in the androgen group compared with placebo. Thus, most of these studies have shown greater strength and performance gains in trained lifters using androgens compared with a placebo.

Androgen Studies: 1980–1990. Considerably less research was conducted investigating ergogenic effects of androgens during this time. However, study designs improved and in some cases were more realistic. Hervey et al. (239) administered 100 $mg \cdot d^{-1}$ of Dianabol (or placebo) to resistance-trained individuals for 6 weeks in a crossover design and reported significant increases in lower- and upper-body strength (but not grip strength) in the androgen group, with no changes during control (placebo) training period. In addition, the androgen group increased body weight and muscle circumferences to a greater extent. These differences were quite substantial between steroid and placebo conditions. It is important to note that in a randomized, crossover design, those who consumed Dianabol initially had

difficulty improving in a subsequent placebo condition. Crist et al. (126) administered testosterone cypionate or nandrolone decanoate (100 mg·wk^{-1}) or placebo to strength-trained men for 3 weeks (plus supplemental protein) and reported nonsignificant differences in peak isokinetic torque and lean body mass. Although subjects in this study reported feelings of greater strength, isokinetic testing did not reveal significant differences. Alen et al. (4,5) examined elite power athletes self-administering anabolic steroids (~31.0 ± 14.3 mg·d^{-1} of methanedienone, stanozolol, and nandrolone, and 178.4 ± 82.7 mg·wk^{-1} of testosterone) for 24 weeks and reported greater increases in muscle fiber area, fat-free mass (FFM), maximal isometric force, and squat strength with androgen use. The increases continued for 6 weeks after the experimental period where no drugs were consumed in the steroid group. In a case study, Häkkinen and Alen (223) reported similar findings where an elite bodybuilder increased FFM, muscle force, and fiber area substantially during a 6-month polydrug regimen and heavy training.

Anabolic Steroid Studies: 1990 to Present. Some studies further examined androgen use in athletes (76). These studies continued to report that cross-sectionally, androgen users had greater strength and muscle mass than nonusers (76), and longitudinally, androgens increased lean body mass, muscle strength, and performance (63,196,203,309). However, a large increase in the number of investigations examining the clinical use of androgens with resistance training occurred during this period, for example, in hypogonadal men, elderly men, and diseased populations. In the U.S.A., most institutional review boards regarded the administration of androgens in nonclinical settings as unethical. Thus, the number of clinical studies rose dramatically while most studies investigating athletic ramifications were performed outside of the U.S.A.

Friedl et al. (196) examined androgen administration of (a) 100 or 300 mg·wk^{-1} of testosterone enanthate or (b) 100 or 300 mg·wk^{-1} of nandrolone for 6 weeks in physically active men. They reported dose-response relationships where the largest gains in body weight and isokinetic muscle strength were seen in most cases with 300 mg·wk^{-1} of testosterone enanthate. Smaller increases in strength were observed with nandrolone administration, although some did not reach statistical significance. Bhasin et al. (63) administered a high dose (600 mg·wk^{-1}) of testosterone enanthate to weight-trained men concomitant with resistance training and reported that the combination of androgen administration plus resistance training produced the largest increases in lean body mass and muscle strength than training with a placebo or just androgen administration alone with no resistance training. Maximum squat and bench press strength increased 38 and 22%, respectively, in the combination group compared with ~20 and 10% increases in the group receiving placebo plus resistance training and group administered androgen only. Bhasin et al. (67), Sinha-Hikim et al. (460), and Storer et al. (482) administered 25, 50, 125, 300, or 600 mg·wk^{-1} of testosterone enanthate (with no resistance training) to resistance-trained men over 20 weeks and reported that increases in lean body mass, type I and II muscle fiber area, and thigh muscle volume were greatest at higher doses, for example, at least 125 mg·wk^{-1}. A positive relationship was seen between lean body mass increases and dose of androgen administered. In addition, muscle strength increased mostly when 50, 300, and 600 mg·wk^{-1} of testosterone enanthate were administered and androgen dose was significantly related to changes in leg press strength. In a follow-up study, Woodhouse et al. (535) reported that changes in muscle size were strongly related to androgen dose. Androgen dose was the best predictor of the anabolic response accounting for 61–65% of the variance in the anabolic response. Kuipers et al. (309) administered 200 mg·wk^{-1} (week 1) and 100 mg·wk^{-1} of nandrolone decanoate (or placebo) to bodybuilders for 8 weeks (along with training) and reported that muscle fiber area increased substantially only in the bodybuilders using steroids. Hartgens et al. (230) also showed a dose-response relationship where they reported that a supraclinical stack of androgens increased deltoid muscle fiber area by 12.6%, whereas administration of a more therapeutic dose (200 mg·d^{-1} of nandrolone decanoate) did not increase fiber area in strength-trained athletes. In a series of studies Hartgens et al. (229), Kuipers et al. (310), and Van Marken Lichtenbelt et al. (512) demonstrated that administration of 100–200 mg·wk^{-1} of nandrolone decanoate for 8 weeks to bodybuilders significantly increased lean tissue mass more than a placebo. Forbes et al. (188) administered ~42 mg·kg^{-1} body mass of testosterone enanthate for 12 weeks in untrained men and reported a large increase in lean body mass. Kouri et al. (304) reported steroid users to have greater body weight and muscle mass. Interestingly, they developed an equation to attempt to predict steroid use based on FFM index. They reported that androgen users had a larger FFM index (e.g., > 25.0). Giorgi et al. (203) administered 3.5 mg·kg^{-1} body mass of testosterone enanthate (or placebo) concomitant to 12 weeks of periodized resistance training and reported greater increases in body weight and bench press strength (22 vs. 9%) in the testosterone group. Much of the gains were lost during a subsequent 12-week period where androgens were not administered. Using a similar administration protocol for 6 weeks, Rogerson et al. (424) reported greater increases in 1 repetition maximum (1RM) bench press strength and cycle sprint performance in the androgen group compared with placebo.

Several studies have investigated androgen administration and performance in elderly (e.g., testosterone replacement), hypogonadal men, and clinical populations. In general, these populations tend to be very responsive as their testosterone concentrations are low and subsequently even low-dose testosterone replacement could have a significant impact. Testosterone replacement has occurred mostly in the forms of oral tablets, intramuscular injections, transdermal patches and

gels, and buccal delivery (373). In hypogonadal young men, several studies have shown that low-dose testosterone replacement of 50–100 mg·wk^{-1} increased lean body mass mostly with minimal strength augmentations (64,69). A meta-analysis in middle-aged men showed that testosterone replacement produced significant increases in lean body mass (2.7%) but only sporadic increases in muscle strength (255). In the elderly, data have been inconsistent as some studies have shown testosterone replacement (typically low dose) alone to increase lean body mass and muscular performance modestly, but others have reported limited effects of testosterone replacement (57,77,85,383). However, there appears to be a dose-response relationship. Bhasin et al. (68) administered 25, 50, 125, 300, or 600 mg·wk^{-1} of testosterone enanthate to elderly men over 20 weeks and reported that increases in lean body mass correlated to the dose administered. In addition, muscle strength increased mostly when at least 125 mg·wk^{-1} of testosterone enanthate was administered, and testosterone dose was significantly related to changes in leg press strength. Schroeder et al. (439) administered 50 or 100 mg·d^{-1} of oxymetholone in elderly men for 12 weeks and reported significant increases in lean body mass and muscle strength. Although the increases in the group receiving 100 mg·d^{-1} of oxymetholone were greater, these data did not reach statistical significance. Limited effects have been shown in some studies with lower doses. Lambert et al. (314) administered 100 mg·wk^{-1} of testosterone enanthate to elderly men over 12 weeks (combined with resistance training) and reported that testosterone replacement did not augment gains in muscle strength and lean body mass.

The effect of androgens on strength and body mass gains has not been lost on the medical community. Many diseases result in weight loss and skeletal muscle atrophy, and the use of androgens to offset these reductions has been suggested. Androgen therapy has been used in patients with human immunodeficiency virus (HIV) infection/AIDS, pulmonary disorders, liver failure, severe burns, renal failure, and spinal cord injuries, and during postoperative recovery. Body mass gains have been common in these studies as a result of androgen therapy (38,112). For example, Casaburi et al. (102) administered 100 mg·wk^{-1} of testosterone enanthate or placebo for 10 weeks in patients with chronic obstructive lung disease (COPD) who were undergoing resistance training simultaneously, and they reported significantly greater increases in lower-body strength and endurance in the testosterone group compared with the placebo group. Interestingly, lean body mass increased similarly in both groups receiving the androgens (e.g., 1 sedentary and 1 resistance training). Strawford et al. (485) investigated the combination of testosterone replacement (100 mg·wk^{-1}) plus resistance training with either a placebo or an additional 20 mg·d^{-1} of oxandrolone for 8 weeks in patients with HIV infection, and they reported the oxandrolone group increased lean tissue mass and several measures of muscle strength to a greater extent than the placebo group. Storer et al. (483) and Bhasin et al. (65) also reported greater increases in lean body mass and strength in HIV-positive men after 12 and 16 weeks of nandrolone (150 mg·wk^{-1}) and 100 mg·wk^{-1} of testosterone enanthate administration, respectively. Interestingly, the addition of resistance training did not augment muscle strength or lean body mass gains when 100 mg·wk^{-1} of testosterone enanthate was administered (65). Bhasin et al. (62) showed 12 weeks of testosterone administration via transdermal patch (2.5 mg every 24 hours) in the absence of resistance training increased lean tissue mass (but not muscle strength) to a greater extent than a placebo in HIV-positive men.

Clinical Applications of Androgens

Testosterone is approved for the treatment of hypogonadism in adult men. The reader is referred to the guidelines for the use of testosterone therapy in hypogonadal men developed by an expert panel of the Endocrine Society (59). Substantial pharmaceutical effort is currently focused on exploiting the anabolic effects of androgens on the skeletal muscle for the prevention and treatment of sarcopenia and functional limitations associated with aging and chronic illness (57), although androgens are currently not approved for these indications.

Testosterone Therapy of Androgen-Deficient Men. Testosterone replacement therapy has been approved by the Food and Drug Administration for the treatment of androgen deficiency syndromes in adult men (59). In young androgen-deficient men, testosterone therapy has many benefits and is associated with a low risk of serious adverse events. Consequently, an expert Panel of the Endocrine Society recommended testosterone therapy for symptomatic men with classical androgen deficiency syndromes who have low testosterone levels (59).

In a systematic review of mostly open-label trials in healthy, androgen-deficient men, testosterone therapy was associated with significant gains in FFM and maximal voluntary strength and a significant decrease in whole-body fat mass (57). Testosterone administration in hypogonadal men also increases vertebral bone mineral density (59). However, its effects on fracture risk are unknown.

Testosterone improves many domains of sexual function in hypogonadal men (60). Testosterone therapy increases spontaneous sexual thoughts and fantasies, overall sexual activity scores and sexual desire (7,24,311,462,476), and attentiveness to erotic stimuli (6). Testosterone administration in healthy, hypogonadal men increases the frequency and duration of nocturnal penile erections (127). Testosterone therapy does not alter the erectile response to visual erotic stimulus (311) or frequency of orgasms in hypogonadal men (59), although it increases the volume of the ejaculate.

The effects of testosterone on mood and sense of well-being have not been well studied. Anecdotally, androgen-deficient men report improvements in sense of well-being and energy

after initiation of testosterone therapy. Testosterone replacement in hypogonadal men improves positive aspects and reduces negative aspects of mood (522). However, randomized clinical trial data on the effects of testosterone therapy on mood are limited and have not shown significantly greater improvements in mood with testosterone therapy than with placebo (476). Some studies have reported small and inconsistent effects of testosterone on visuospatial cognition and verbal memory and verbal fluency (106,261).

Studies of the effects of testosterone therapy on insulin sensitivity have yielded conflicting results (249,281,343, 344,456). Although low testosterone levels in cross-sectional studies of community-dwelling men have been associated with increased risk of insulin resistance and type 2 diabetes mellitus, testosterone therapy has not been shown consistently to improve insulin sensitivity or risk of diabetes mellitus in randomized clinical trials.

Adverse Events Associated With Testosterone Replacement Therapy. There is an agreement that testosterone therapy of young hypogonadal men is associated with a low frequency of adverse events (59). Acne and oiliness of skin are common in young hypogonadal men. Erythrocytosis is the most frequent and dose-limiting adverse event associated with testosterone therapy in testosterone trials (59). The increments in hematocrit during testosterone therapy are related to testosterone dose and age (122); older men experience greater increments in hemoglobin and hematocrit than young men (122).

The frequency of the development of gynecomastia in testosterone-treated men is low. Testosterone has been reported to induce and worsen obstructive sleep apnea. Patients with obstructive sleep apnea have a high frequency of low testosterone levels and testosterone therapy has also been reported to improve sleep apnea.

Testosterone therapy in young hypogonadal men increases prostate-specific antigen (PSA) levels by an average 0.3 $ng \cdot mL^{-1}$ and in older hypogonadal men by 0.43 $ng \cdot mL^{-1}$ (95). However, PSA levels do not increase progressively during continued testosterone therapy (46,350). Similarly, hypogonadal men have smaller prostate volumes than age-matched eugonadal controls (46,350). After initiation of testosterone therapy, prostate volume increases to that seen in age-matched eugonadal controls. There is no evidence that testosterone therapy worsens lower urinary tract symptoms or causes prostate cancer. However, testosterone administration might promote the growth of metastatic prostate cancer. Many older men harbor subclinical prostate cancers in their prostate; there is concern that testosterone therapy of older men might induce these subclinical cancers to grow and become clinically overt (59,61). Testosterone therapy is associated with increased risk of prostate biopsy and detection of prostate events (59,61).

Contraindications for Testosterone Therapy. Testosterone therapy is contraindicated in men with prostate and breast cancer (59). Testosterone is associated with high risk of serious adverse events in men with erythrocytosis, untreated severe sleep apnea, severe lower urinary tract symptoms as indicated by AUA/IPSS symptom score greater than 19, or class III or IV congestive heart failure. Testosterone therapy should not be initiated in individuals with undiagnosed prostate nodule or induration or PSA more than 3 $ng \cdot mL^{-1}$ without appropriate urological evaluation (59).

Monitoring of Testosterone Therapy. The goal of testosterone therapy is to raise testosterone levels into the mid-normal range for healthy young men, correct symptoms of androgen deficiency, induce and maintain secondary sex characteristics, and maintain sexual function (59). Testosterone levels should be measured 3 months after initiating testosterone therapy and the dose and/or regimen adjusted to achieve testosterone levels in the mid-normal range.

To minimize risks and for early detection of adverse events, the Endocrine Society Expert Panel recommended that patients receiving testosterone therapy should have their hematocrit and serum PSA, and AUA/IPSS prostate symptoms score measured before initiating therapy, 3 months after starting therapy, and annually thereafter (59). The patients should also undergo digital prostate examination at baseline, after 3 months of therapy, and annually thereafter. Androgen-deficient men should undergo a dual x-ray absoriptiometry (DEXA) scan to measure baseline bone mineral density; patients deemed osteoporotic should have their bone mineral density measured again by DEXA scan 1 or 2 years after initiating testosterone therapy.

Testosterone Therapy for Sexual Dysfunction. Many domains of male sexual function are regulated by testosterone (60). Pioneering investigations have demonstrated that androgen-deficient men can achieve penile erections in response to erotic stimuli, but their overall sexual activity is decreased (332,476). Testosterone increases sexual thoughts, desire (311), arousal, and attentiveness to erotic stimuli (6). Testosterone administration increases the frequency, fullness, and duration of nocturnal penile tumescence (96). Maximum rigidity may require a threshold level of androgen activity (92): testosterone regulates nitric oxide synthase (NOS) in the cavernosal smooth muscle (332) and exerts trophic effects on cavernosal smooth muscle (446) and ischiocavernosus and bulbospongiosus muscles, and is necessary for the veno-occlusive response. However, testosterone does not improve erectile response to visual erotic stimulus (311) or erectile function in men with erectile dysfunction who have normal testosterone levels or orgasms (258).

Androgen deficiency and erectile dysfunction are 2 independently distributed disorders that coexist in 6–10% of middle-aged and older men (300). Testosterone trials among sildenafil failures have been inconclusive (26,447). There is insufficient evidence to support the proposal that testosterone improves therapeutic response to selective phosphodiesterase inhibitors (26,59,447).

Table 4 provides the domains of sexual function that are improved by androgen therapy in hypogonadal men. Systematic reviews of randomized trials have shown that testosterone therapy improves sexual activity and libido in men with sexual dysfunction who have unequivocally low testosterone levels but not in men with normal testosterone levels. These considerations led the Endocrine Society Expert Panel to "suggest (that) clinicians offer testosterone therapy to men with low testosterone levels and low libido in order to improve libido and to men with erectile function (ED) who have unequivocally low testosterone levels after evaluation of underlying causes of ED and consideration of established therapies for ED)" (59). However, the expert panel noted the low-quality evidence supporting this suggestion.

Anabolic Applications of Androgens for the Prevention and Treatment of Sarcopenia and Functional Limitations Associated With Aging and Chronic Illness. Administration of supraphysiologic doses of testosterone increases skeletal muscle cross-sectional area, lean body mass, and maximal voluntary muscle strength in eugonadal young men (Figure 3) (63). Subsequent research has shown that the anabolic effects of testosterone on appendicular skeletal muscle mass, muscle size, and maximal voluntary strength are correlated with the administered dose and circulating testosterone concentrations (Figure 4) (68). This section will review possible clinical applications of testosterone therapy to treat the muscle wasting and functional limitations associated with aging and chronic diseases.

Mechanisms of Testosterone Effects on the Skeletal Muscle. Testosterone-induced increase in skeletal muscle mass is associated with hypertrophy of both type I and type II fibers (460) and an increase in the number of myonuclei and satellite cells (461). Testosterone promotes the differentiation of mesenchymal multipotent cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage (66,459). Androgens regulate mesenchymal multipotent cell differentiation by binding to AR and promoting the association of AR with β-catenin and translocation of the AR–β-catenin complex into the nucleus, resulting in activation of TCF-4 (458). The activation of TCF-4 modulates a number of Wnt-regulated genes that promote myogenic differentiation and inhibit adipogenic differentiation (458).

Testosterone also inhibits preadipocyte differentiation into adipocytes (458). The effects of testosterone on myogenic differentiation in vitro are blocked by the AR antagonist, bicalutamide, indicating that these effects are mediated through an AR pathway (458). It is possible that androgens might exert additional effects through nongenomic mechanisms. Testosterone increases fractional muscle protein synthesis and improves the reutilization of amino acids by the muscle (180–182,447).

We do not know whether conversion of testosterone to DHT or to estradiol 17-β is required for mediating androgen effects on the muscle. Steroid 5-α reductase (SRD5A2), which converts testosterone to DHT, is expressed at low concentrations in skeletal muscle, but individuals with congenital SRD5A2 deficiency have normal muscle development at puberty.

Androgen Therapy in Chronic Diseases. Low testosterone is a common feature of many chronic diseases in men and is associated with loss of muscle mass and strength, bone density, sexual dysfunction, and loss of energy (276). The observations that androgen replacement or supplementation unequivocally increases FFM, total body mass, and maximal voluntary strength in hypogonadal men and healthy, eugonadal young and older men have led to the hypothesis that androgens might be useful in treating the loss of muscle and physical function seen in patients with chronic diseases such as HIV infection with wasting syndrome, COPD, and end-stage renal disease (ESRD).

Testosterone Therapy for HIV-Infected Men With Weight Loss. There is a high prevalence of low testosterone levels in HIV-infected men, even among those receiving highly active antiretroviral therapy (25,153,423). Serum testosterone levels are lower in HIV-infected men with weight loss (120) and correlate with deficits in muscle mass and strength (65,62,215,483), low Karnofsky scores (25), depressed mood, and disease progression (218,412,433).

Some of the studies that have examined the effects of androgen administration on body weight and composition in HIV-infected men were not placebo controlled (54,205,235, 413) and most failed to control energy intake and exercise stimulus. Three placebo-controlled studies of testosterone supplementation of HIV-infected men (62,65,482) reported gains in FFM, whereas others (119,152) did not. Significantly greater improvements in maximal voluntary strength have been shown in HIV-infected men treated with androgens vs. placebo (65,216,217,485). In a recent meta-analysis, testosterone therapy had a moderate effect on depression (−0.6 *SD* units, 95% confidence interval [CI] −1.0, −0.2), but no significant testosterone effect on quality of life (58). There were no

Table 4. Domains of sexual function that are improved by testosterone therapy of androgen-deficient men.*

1. Spontaneous sexual thoughts
2. Attentiveness to erotic auditory stimuli
3. Frequency of nighttime and daytime erections
4. Duration, magnitude, and frequency of nocturnal penile erections
5. Overall sexual activity scores
6. Volume of ejaculate

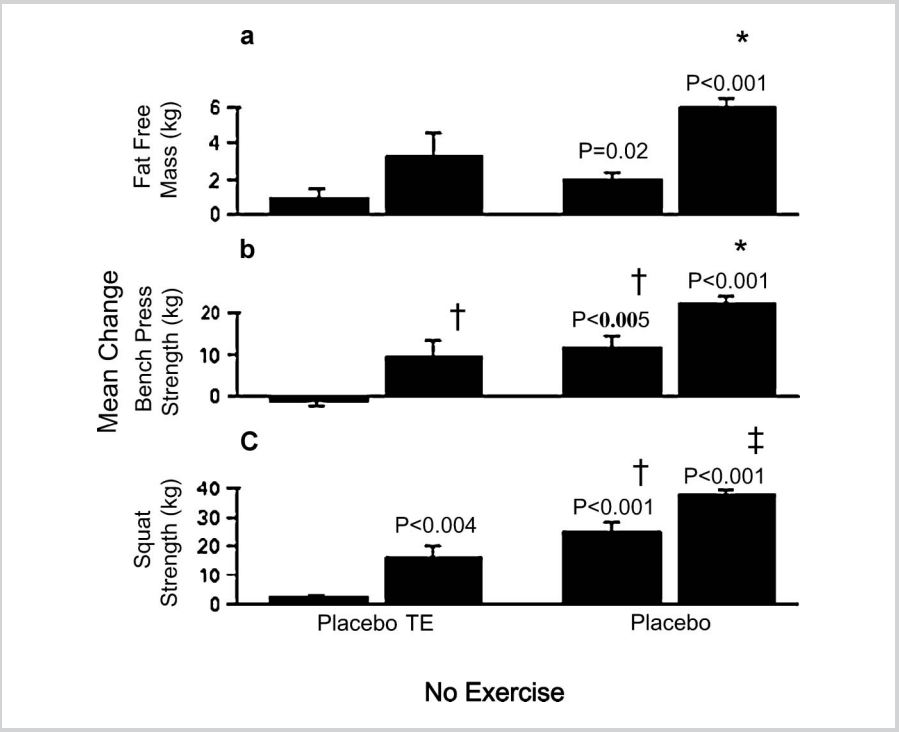


Figure 3. Changes from baseline in mean (±*SE*) fat-free mass (a) and muscle strength in the bench press (b) and squatting exercises (c) over the 10 weeks of treatment with 600 mg·wk^{-1} testosterone enanthate (TE). The *p* values shown are for the comparison between the change indicated and a change of zero. *$p < 0.05$ for the comparison between the change indicated and that in either no-exercise groups; †$p < 0.05$ for the comparison between the change indicated and that in the group assigned to placebo with no exercise; ‡$p < 0.05$ for the comparison between the change indicated and the changes in all 3 other groups. Modified from Bhasin et al. (65).

significant differences in adverse event rates or changes in CD4$^+$ T lymphocyte counts, HIV viral load, PSA, and plasma HDL cholesterol between testosterone- and placebo-treated men with HIV infection (58).

Testosterone trials in HIV-infected men have been small and characterized by heterogeneity across trials. There are no data on testosterone's effects on physical function and risk of disability or its long-term safety. Overall, short-term (3–6 months) testosterone use in HIV-infected men with low testosterone levels and weight loss can lead to small gains in body weight and lean body mass (LBM) with minimal change in quality of life and mood. This inference is weakened by inconsistent results across trials. These considerations led the Endocrine Society Expert Panel to "suggest (that) clinicians consider short-term testosterone therapy as an adjunctive therapy in HIV-infected men with low testosterone levels and weight loss in order to promote weight maintenance and gains in LBM and muscle strength" (59). The evidence supporting this suggestion is of moderate quality.

Chronic Obstructive Pulmonary Disease. Patients with COPD have weak muscles (55,209,480) with smaller cross-sectional area (55) than age- and gender-matched healthy individuals. Mid-arm area (468), mid-thigh cross-sectional area (345), and quadriceps strength (490) have been shown to be predictors of mortality in patients with COPD. Peripheral muscle weakness in patients with COPD is associated with increased utilization of health care resources (131). Proposed mechanisms of skeletal muscle dysfunction in COPD are numerous and include disuse atrophy, systemic inflammation, oxidative stress, blood gas abnormalities, and use of glucocorticosteroids (11,100,101,421,521). Several studies have reported higher prevalence of low testosterone in men with COPD than in healthy older men (100,101, 513), although a study reported frequency of low testosterone levels to be no greater than healthy age-matched controls (312).

Resistance exercise training improves skeletal muscle strength (56,102,400,455,480) and leg extensor power in patients with COPD (245). Only scant evidence (400), however, suggests that these changes result in improvement of physical function. Recent evidence-based guidelines for pulmonary rehabilitation (371,422) have emphasized the value of resistance exercise training for increasing muscle strength and muscle mass for both upper and lower extremities.

Five studies, including 4 randomized placebo-controlled trials, have investigated the effect of androgens in patients with COPD (102,125,183,438,542). Schols et al. (438) reported a 1.5 kg weight gain over 8 weeks in 217 men and women with COPD. Subjects receiving nandrolone decanoate (women, 25 mg; men 50 mg) plus nutritional and exercise interventions increased FFM to a greater extent than those receiving placebo plus the nutritional supplement and exercise ($p < 0.03$). Fat mass increases accounted for most of the weight gain in the placebo group. No differences in respiratory muscle strength between groups were noted. Similarly, Creutzberg and et al. (125) showed that men with COPD receiving 8 weeks of biweekly injections of 50 mg nandrolone decanoate experienced significantly greater increase in DEXA-determined FFM when compared with controls, 1.7 ± 2.5 vs. 0.3 ± 1.9 kg, respectively. Muscle function and exercise capacity improved to the same extent

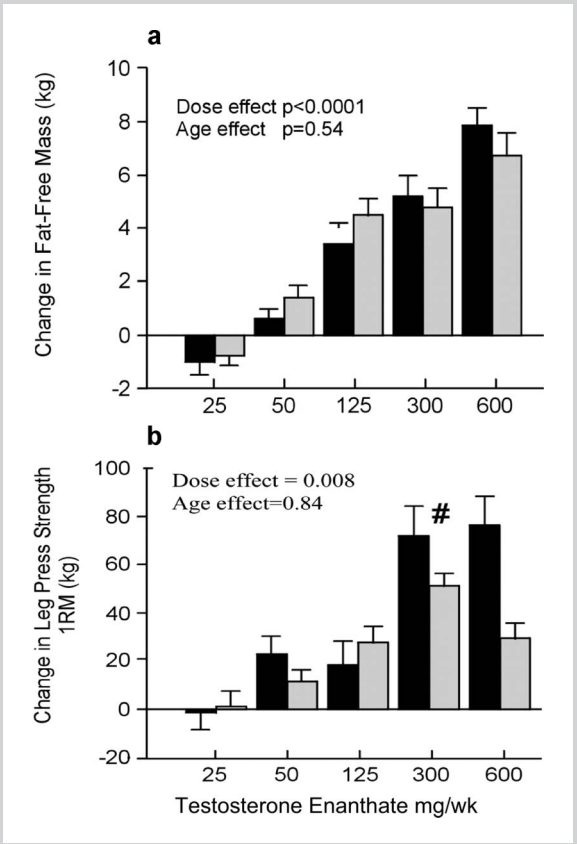


Figure 4. Changes from baseline in fat-free mass (a) and leg press strength (b) in young (■) and older (▨) men in response to graded doses of testosterone enanthate. Healthy, young, and older men were randomized to receive a long-acting gonadotropin-releasing hormone agonist plus one of 5 different doses of testosterone enanthate (25, 50, 125, 300, and 600 mg weekly, intramuscularly) for 20 weeks. Changes in other outcome measures were calculated as the difference between week 20 and baseline values. Data are the mean ± *SEM*. If there were a significant age effect, the values for young and older men for each dose were compared using Tukey's multiple comparison procedure. Similarly, if the linear model revealed a significant dose effect, then different dose groups were compared using Tukey's multiple comparison procedure. #significant difference from 25- and 50-mg doses ($p < 0.05$). Modified from Bhasin et al. (68).

in both groups. Ferreira et al. (183) reported that underweight patients with COPD increased lean body mass by 2.5 kg after 6 months of treatment with 12 mg·d^{-1} oral stanozolol. Neither the stanozolol nor the control group demonstrated functional improvements or changes in maximum inspiratory pressure. In a multicenter, open-label trial of oral oxandrolone in men and women with COPD, Yeh et al. (542) showed an average 2.1 kg weight gain (1.6 kg lean mass) after 4 months of treatment. Neither spirometry nor 6-minute walk distance changed significantly.

Casaburi et al. (102) were the first to demonstrate significant increases in muscle performance, as well as increases in lean body mass after androgen administration in men with COPD. Using a 2-by-2 factorial design, 47 men with moderate to severe COPD (mean forced expiratory volume in the first second of expiration = 40% of predicted) and low testosterone (mean = 320 ng·dL^{-1}) were randomized to one of 4 groups in a 10-week study: resistance exercise training only, resistance training + placebo, resistance training + 100 mg·wk^{-1} testosterone enanthate, or 100 mg·wk^{-1} testosterone enanthate only. Men receiving testosterone had mean nadir levels within the mid-range of young healthy men. Leg press strength increased 17% in the men receiving testosterone alone and in the resistance training plus placebo groups; leg press strength improved 27% in the combined group. Leg press fatigability (repetitions to failure at 80% 1RM) increased by 2, 7, and 11 repetitions, in the testosterone only, resistance training + placebo, and combined groups, respectively. Lean body mass increased 2.3 kg in the testosterone-only group and 3.3 kg in the group receiving testosterone + resistance exercise training. No changes in lean body mass were noted in the men who only performed resistance training only. Thus, 10 weeks of a replacement dose of testosterone in men with moderate to severe COPD yielded significant improvements in lean body mass, muscle strength, and resistance to fatigue. Resistance training of the legs resulted in benefits similar to testosterone and the combination of the interventions proved to be additive.

Increased strength and resistance to fatigue might prove valuable in maintaining physical function required in activities of daily living. Because muscle cross-sectional area predicts mortality in patients with COPD (345), interventions that stimulate increased muscle mass would be expected to improve outcomes. However, small sample size, substantial heterogeneity across trials, relatively small androgen doses, and the lack of inclusion of patient-important outcomes in these trials contributed to the weak quality of available evidence and preclude a general recommendation about testosterone therapy in men with COPD at this time.

Testosterone Therapy in Glucocorticoid-Treated Men. Glucocorticoid administration in pharmacologic doses is associated with muscle atrophy and a high frequency of low testosterone levels (278,336,416,417) due to suppression of all components of the hypothalamic-pituitary-testicular axis. In 2 randomized placebo-controlled trials (54,418), testosterone supplementation of men receiving glucocorticoid treatment for bronchial asthma or chronic obstructive pulmonary disease was associated with an average 2.3 kg (95% CI 2.0–3.6) greater gain in lean body mass and a greater decrease in fat mass (contrast −3.1 kg, 95% CI −3.5, −2.8) than placebo (57). These 2 trials (54,418) found an increase in bone mineral density in the lumbar spine (+4%, 95% CI 2–7%); the effect on femoral bone density was inconsistent and not significant (57). There are no data on the effects of testosterone supplementation on bone fractures in glucocorticoid-treated men. Testosterone administration was associated with a low frequency of mild adverse events (124,418). Based on

such data, the Endocrine Society Expert Panel suggested (59) that "clinicians offer short-term testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels in order to promote preservation of LBM and bone mineral density" (59). These inferences are weakened by the small size of the studies, high rates of loss to follow-up in 1 study, and inconsistent results (57,59).

End-Stage Renal Disease. Approximately two-thirds of men receiving dialysis for treatment of chronic renal failure have low testosterone levels (3,457). Hypogonadism in men with ESRD has been associated with sexual dysfunction (385), osteoporosis risk (3), anemia (86), and malnutrition (189). Carotid artery intimal thickness and presence of atherosclerotic plaque have been shown to be negatively correlated with serum testosterone levels in patients with ESRD but positively related to endothelium-dependent vasodilation (282).

Exercise intolerance and malaise are common problems among many individuals undergoing maintenance hemodialysis (MHD) (252). Studies of exercise capacity and training in these patients frequently report low exercise tolerance (32,263,384,481), muscular weakness, low physical activity levels (268), and impaired physical function (73,266,267, 271,299). Johansen et al. (271) have demonstrated that dialysis patients have significantly greater contractile area atrophy compared with healthy controls, even when corrected for habitual activity level. The muscle atrophy was associated with muscle weakness and reduced gait speed (271). Abnormalities in muscle function and physical performance begin early in the course of chronic kidney disease (CKD), become progressively worse as the disease progresses (318), and are a major determinant of self-reported quality of life in patients with ESRD (111).

Functional limitations in patients with ESRD are undoubtedly multifactorial; low levels of anabolic hormones such as testosterone and GH, physical inactivity, uremic myopathy, malnutrition, and carnitine deficiency have been proposed as contributors (138,271,299,302).

Strategies to increase muscle mass and strength are attractive because they would be expected to improve physical function and quality of life. Exercise training including endurance training, resistance training, and their combination, and androgens are possible approaches that may be used to overcome muscle atrophy and weakness.

Johansen et al. (269) demonstrated that 6 months of weekly injections of 100 mg nandrolone decanoate significantly increased lean body mass by 4.5 ± 2.3 kg compared with the 1.9 ± 0.6 kg change in the placebo group. Muscle mass increases were observed only in the nandrolone-treated men. Combined times for completing walking and stair climbing tasks decreased by 3.8 seconds in the treated group compared with a 3.4-second increase in control subjects; these differences were statistically significant. There were no differences in the change in grip strength between the 2 groups.

In a recent 12-week, randomized controlled trial of nandrolone decanoate (100 mg·wk^{-1} for women, 200 mg·wk^{-1} for men) or placebo with or without resistance exercise training, Johansen et al. (270) confirmed their earlier findings of significantly increased LBM, 3.3 ± 2.0 kg with nandrolone treatment alone. The subjects receiving nandrolone in combination with resistance training also experienced significant gains in LBM, 3.0 ± 2.4 kg. Lean body mass did not change in either of the placebo-controlled groups. Quadriceps cross-sectional area increased significantly in both the nandrolone and exercise groups relative to the controls and was additive in the combined treatment group. Training-specific 3RM strength measures for the lower extremity improved only in the groups receiving resistance training. These effects on muscle size, strength, and body composition were not different between men and women. Neither intervention, alone or in combination, produced significant changes in measures of physical function, for example, gait speed, stair climbing, or chair stands. It is possible that the short study duration may have not allowed sufficient time for the neuromuscular adaptations that are necessary for translation of muscle mass and strength gains into functional improvements. Self-reported improvements in physical function were noted in the resistance-trained group but not in the nandrolone group. The doses of nandrolone decanoate used in this study were well tolerated. With 79 patients randomized (49 men) and an 86% completion rate, this was the largest randomized controlled trial to date using androgens or resistance exercise training in patients undergoing MHD. Even so, the study may not have had sufficient power to detect clinically meaningful changes in measures of physical function.

Eiam-Ong et al. (162) randomized 29 predialysis patients with CKD in a 3-month investigation of the anabolic effects of nandrolone decanoate. Subjects received either conventional treatment for CKD or conventional treatment plus weekly injections of 100 mg nandrolone. Lean body mass increased significantly greater in the nandrolone-treated group as compared with controls, 2.1 ± 2.2 vs. 0.4 ± 1.4 kg, respectively. The authors concluded that 100 mg·wk^{-1} nandrolone decanoate significantly improved lean body mass without altering renal function or producing serious adverse effects in these patients.

The ideal dose of nandrolone decanoate for anabolic effects in patients with chronic kidney failure has not been determined, and there is only limited evidence that changes in muscle size and strength in these patients can translate into functional improvements after androgen administration. Improvements in self-reported physical function, although not currently seen in studies of hemodialysis patients receiving androgen administration, are nevertheless important with respect to its association with lower morbidity and mortality in these patients (330). Additional adequately powered studies are needed to determine whether long-term treatment with androgens is safe and effective in improving physical function (both measured and self-reported),

mobility, and health-related outcomes, and in reducing morbidity and mortality in patients with ESRD.

Testosterone Therapy for Older Men With Sarcopenia and Functional Limitations. Cross-sectional as well as longitudinal studies are in agreement that total and free testosterone concentrations decline progressively with advancing age (32,128,178,184,212,228,363,401,404,454,550). In the Baltimore Longitudinal Study on Aging, 20% of men older than 60 years and 50% of men older than 80 years had total testosterone levels in the hypogonadal range (total testosterone less than 325 ng·dL^{-1}) (228). Because SHBG concentrations are higher in older men than in young men (178,401), free testosterone concentrations decline to a greater extent than total testosterone concentrations. The age-related decline in testosterone concentrations is the result of defects at all levels of the hypothalamic-pituitary-testicular axis.

In epidemiological studies (44,45,354,361,376,382,394,428, 436,510), low total or bioavailable testosterone levels are associated with low appendicular skeletal muscle mass and muscle strength and self-reported physical function. Low testosterone levels have also been associated with decreased self-reported and performance-based physical function in a number of epidemiologic studies (130,361,376, 382,436,510). The data on the association of testosterone levels with sexual dysfunction have been inconsistent (17,275,300,341,502,549). In general, serum total and bioavailable testosterone levels are not significantly different between men who report erectile dysfunction and those who do not (275,300). In the Massachusetts Male Aging Study (MMAS), decreased libido, as assessed by a single question, was associated only with very low testosterone levels (502). In another study of men older than 50 years who had benign prostatic hyperplasia, sexual dysfunction, assessed by the Sexual Function Inventory, was reported only in men with serum total testosterone levels less than 225 ng·dL^{-1} (341).

Age-related declines in verbal memory, visual memory, spatial ability, and executive function are associated with the age-related decline in testosterone (6,35,109,177,210,240,260,261,452,496).

The relationship of testosterone levels with depression has been inconsistent across epidemiologic studies (36,137,342, 443,444,511). Low testosterone levels in older men appear to be associated more with subsyndromal depression and related symptoms than with major depression (443,444). In one study, testosterone levels were lower in older men with dysthymic disorder than in those without any depressive symptoms (443). In another study, men with low testosterone levels had higher Carroll Rating Index scores, indicating more depressive symptoms than those who had normal testosterone levels (137).

Several epidemiologic studies of older men (12,165,214, 317,354), including MrOS (165), the Rancho Bernardo Study (214), the Framingham Heart Study (12), and the Olmsted County Study (354), have found bioavailable testosterone levels to be associated with bone mineral density, bone geometry, and bone quality (317); the associations are stronger with bioavailable testosterone and estradiol levels than with total testosterone levels. In the MrOS Study, the odds of osteoporosis in men with a total testosterone less than 200 ng·dL^{-1} were 3.7-fold higher than in men with normal testosterone level (165); free testosterone was an independent predictor of prevalent osteoporotic bone fractures (352).

Several recent studies have evaluated the association of testosterone levels and mortality; 2 Veterans Administration (VA) studies (450,451) and the Rancho Bernardo Study (316) found higher overall all-cause mortality in men with low testosterone levels than in those with normal testosterone levels, but testosterone levels were not correlated with overall mortality in the MMAS (18). In the Rancho Bernardo Study, men in the lowest quartile of testosterone levels ($<$241 ng·dL^{-1}) were 40% more likely to die over the next 20 years than those with higher levels (316). The increased risk of death in men with low testosterone levels was independent of multiple risk factors, including age, adiposity, and lifestyle (316).

Testosterone levels are not correlated with aging-related symptoms assessed by the Aging Male Symptom score or with lower urinary tract symptoms assessed by the AUA/IPSS prostate symptom questionnaire (323). A number of cross-sectional studies also found no difference in serum testosterone levels between men who had coronary artery disease and those who did not have coronary artery disease; other studies have reported testosterone levels or to be lower in men with coronary artery disease than in men without coronary artery disease (8,34,118,222,540). A cause and effect relationship cannot be inferred from these epidemiological studies, especially cross-sectional studies. Furthermore, even the associations between testosterone levels and health-related outcomes that have been found to be statistically significant are weak.

The risks and health benefits of long-term testosterone remain poorly understood. Overall, testosterone trials in older men have been characterized by small sample size, inclusion of healthy older men with low or low-normal testosterone levels who were asymptomatic, and the use of surrogate outcomes; these studies did not have sufficient power to detect meaningful gains in patient-important outcomes and changes in prostate and cardiovascular event rates (13,72,85, 163,182,290,365,383,453,465,497,506,534).

In a systematic review of randomized trials (57), testosterone therapy was associated with a significantly greater increase in FFM (contrast 2.5 kg, 95% CI 1.5–3.4) and right hand grip strength (contrast 3.3 kg, 95% CI 0.7–5.8 kg) (Figure 5). Whole-body fat mass showed a greater reduction in androgen groups (contrast −2.1 kg, 95% CI −3.1, −1.1) than in placebo (163,182,290,364,383,465,497,534).

Testosterone therapy also improves self-reported physical function, assessed by the physical function domain of MOS SF-36 questionnaire (0.5 *SD* units, 95% CI 0.03–0.9) (57,59).

However, the effects of testosterone replacement on quadriceps strength, leg power, muscle fatigability, and physical function in older men have been inconsistent across trials, and its effects on risk of disability and falls have not been studied (39,163,365,383). Testosterone replacement increases lumbar bone mineral density but not femoral bone mineral density in older men with low testosterone levels (13,290,465), but we do not know whether testosterone reduces fracture risk. Testosterone replacement improves sexual function in older men with low testosterone levels (74,254) but not in men with erectile dysfunction who have normal testosterone levels. Testosterone therapy has been shown to improve visual-spatial skills, verbal memory, and verbal fluency in older men with low testosterone levels in some but not in all trials. It is unknown whether testosterone supplementation can induce clinically meaningful changes in cognitive function in older men. The effects of testosterone replacement on vitality and health-related quality of life have not been studied. Short-term administration of testosterone in replacement doses is safe, but the long-term risks of testosterone administration in older men remain unknown.

The potential adverse effects of testosterone in older men include the risk of erythrocytosis, induction or exacerbation of sleep apnea, gynecomastia, and clinically detectable prostate events. Testosterone administration by increasing the intensity of PSA surveillance will likely lead to increased number of prostate biopsies and increased detection of prostate cancers (95). It is possible that testosterone administration might make subclinical foci of prostate cancer grow and become clinically overt; we do not know what clinical impact this would have on patient morbidity and survival and health care costs (57,59). Because the efficacy of testosterone supplementation on health-related outcomes has not been demonstrated and its risks remain largely unknown, an expert panel of the Endocrine Society concluded that the available data did not permit a general recommendation about testosterone therapy for all older men with low testosterone levels (59). The panel suggested that until more information becomes available, testosterone administration in older men should be individualized and limited only to older men with unequivocally and consistently low testosterone levels who are experiencing significant symptoms of androgen deficiency; in these individuals, consideration of testosterone therapy should be preceded by a careful discussion of its potential risks and benefits with the patient and rigorous monitoring of potential adverse effects (59). An expert panel of Institute of Medicine on the Future Direction of Testosterone Research deemed this a priority area for further research and recommended coordinated trials of testosterone therapy in symptomatic older men in 4 efficacy areas: physical dysfunction, sexual dysfunction, vitality, and cognitive dysfunction (325).

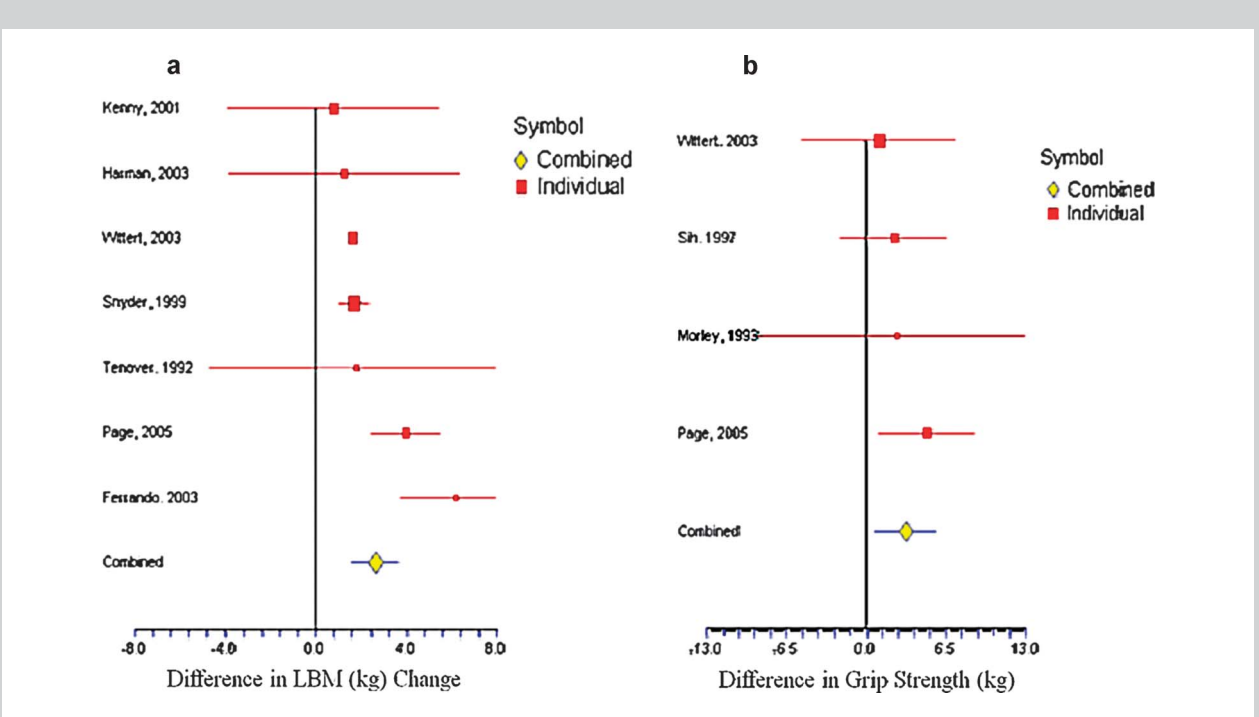


Figure 5. Changes in LBM and grip strength. Meta-analysis plots of contrasts between testosterone-treated and placebo-treated men older than 45 years. (a) The change in lean body mass (kg). (b) The change in right hand grip strength. A positive difference indicates a favorable testosterone effect. Confidence intervals that do not overlap with zero represent significant differences between placebo and testosterone groups. Modified from Bhasin et al. (58).

Dosing and Use Patterns of Androgens in Athletic Populations

Androgens are typically used by athletes in a "stacking" fashion, in which several different drugs are administered simultaneously. The basis for stacking is that the potency of one anabolic agent may be enhanced when consumed simultaneously with another anabolic agent. Athletes will typically use both oral and parenteral (injectable) compounds; however, the administration of androgens via injection appears to be the most common method of self-administration (as indicated by 77% of androgen users) (114). The primary reason for using parenteral compounds is thought to be related to health reasons and the belief that this route of administration results in greater results (114). Most users will take androgens in a cyclic pattern, meaning they will use the drugs for several weeks or months and alternate these cycles with periods of discontinued use. Often athletes will administer the drugs in a pyramid (step-up) pattern in which dosages are steadily increased over several weeks. Toward the end of the cycle, the athlete will "step down'" to reduce the likelihood of negative side effects. At this point, some athletes will discontinue drug use or perhaps initiate another cycle of different drugs (i.e., drugs that may increase endogenous testosterone production to prevent the undesirable drop in testosterone concentrations that follows the removal of the pharmaceutical agents). Although the length of each cycle is quite variable (ranges from 1 to 728 weeks), the median cycle length is reported to be 11 weeks (114). Recent surveys have indicated that the typical nonmedical use pattern is 4–6 months in a year (114,388). A typical androgen regimen involves 3.1 agents, and the dose being administered is reported to vary between 5 and 29 times greater than physiological replacement doses (395). Nearly 50% of individuals who self-administer androgens exceed 1,000 mg of testosterone or its equivalent per week (388). However, this number may be exaggerated, as Cohen et al. (114) in a more recent survey suggested that the number of androgen users who self-administer more than 1,000 mg of testosterone or its equivalent per week may be closer to 10%. Regardless, the higher pharmacologic dosages common among androgen users do appear to be important for eliciting the gains that these individuals desire. The importance of dose has been clearly demonstrated in a classical study published by Forbes in 1985 (187), in which total dose of androgens administered was shown to have a logarithmic relationship to increases in lean body mass. These results provide fuel to the more is better philosophy employed by many athletes using performance-enhancing drugs.

Another issue associated with androgens use is the polypharmacy that is often seen among individuals who self-administer these drugs. A recent study indicated that 96% of androgen users (481 of 500) admitted to using other anabolic agents and/or stimulants to exacerbate the performance gains or medications to reduce the side effects associated with androgen use (388). The most common type of accessory medication used by these individuals appears to be compounds designed to promote fat loss. More than 65% of users admit to using caffeine and ephedra/ephedrine during their drug cycle. In addition, one of every 4 individuals who admit to self-administering androgens also indicated that they concomitantly use GH, insulin, or IGF during their drug cycle (388). More than half of individuals who self-administer androgens also use medications to reduce or prevent side effects generally associated with androgen abuse (388).

Masking Agents and Drugs Commonly Used with Androgens

In many cases, androgens are consumed along with other drugs as part of a "stack" or to mask steroid use in preparation for drug testing. Likewise, these drugs are banned substances that can result in a positive drug test and subsequent punishment. The following section briefly examines some other drugs that athletes may use in addition to androgens and hGH.

Masking Agents. Masking agents are used to produce negative drug testing results by hiding the use of androgens and other drugs. In some cases, diuretics have been used to dilute urine and mask drug use. Sulfonamides decrease the excretion rate of various drugs and are used to slow the excretion rate of androgens metabolites. However, these drugs were more effective when drug testing was more primitive in its development. Current drug tests can detect anabolic steroids in the urine despite the use of sulfonamides. One commonly used sulfonamide, probenecid, has been added to the banned substances list, and its use has declined dramatically among athletes. Probenecid was developed in the 1950s to reduce the excretion of penicillin. Detection of probenecid results in a failed drug test and possible suspension.

Some athletes have also used epitestosterone as a masking agent (2). Epitestosterone is 17α epimer of testosterone found in urine in similar concentrations to testosterone. Although its physiological role is unclear (e.g., possible antiandrogenic activity) (474), some athletes have administered epitestosterone (in similar doses to their testosterone regimen) to reduce the T:E ratio to within legal limits (i.e., a 4:1 ratio). Reports from athletes have indicated that epitestosterone injections 1 hour before testing have resulted in a "passed" drug test. Although epitestosterone administration can be detected (2), it could result in an athlete passing a drug test unless it is specifically tested for. Epitestosterone is difficult to obtain commercially so it is mostly used by elite athletes. Last, other masking procedures such as urine substitution, catheterization, use of adulterants, and other tampering methods have been reported (257). These procedures are banned, and stricter enforcement policies have been used in an attempt to decrease their use among athletes.

Diuretics. Diuretics block sodium reabsorption in the kidneys and induce fluid and electrolyte loss in urine. Diuretics have been used to treat diseases such as hypertension, congestive

heart failure, edema, and kidney and liver problems (80,241,492). Classifications include loop diuretics (block sodium reabsorption in the loop of Henle in the kidneys, that is, furosemide, bumetanide, ethacrynic acid, torsemide), thiazides (block sodium reabsorption at the distal tubule, i.e., chlorthalidone, hydrochlorothiazide, indapamide, metolazone, trichlormethiazide, quinethazone), and potassium--sparing diuretics (i.e., amiloride, triamterene, spironolactone). Other types of diuretics exist but are much less commonly used by athletes. Diuretics induce fluid/weight loss, have been used as masking agents for androgen tests by athletes (reduce the concentration of drugs in the urine via rapid diuresis), and have been used in sports that used weight classes and bodybuilding. Benzi (53) has reported that diuretics were the fourth most commonly used drug behind androgens, stimulants, and narcotics. Diuretics are banned substances, and urine samples containing diuretic residues result in a failed drug test.

Diuretics are used in the short-term. They pose many other serious side effects including fatigue, weakness, muscle cramps, soreness, headaches, confusion, nausea, loss of appetite, cardiac arrhythmia, and reduced muscle glycogen. Studies have shown that 40–126 mg of furosemide resulted in 2–4% losses in body weight and subsequent reductions in cycling performance, $\dot{V}O_2$max, muscle strength, and rate of force development (23). Aerobic exercise performance appears to be more highly reduced than anaerobic exercise performance, as some studies have shown some reductions in strength and power but others have shown no performance decrement with mild dehydration (33). A recent study has shown that 40 mg of furosemide (resulting in a 2.2% reduction in body weight) did not negatively affect 50-, 200-, or 400-m sprint times or vertical jump height (525).

Antiestrogens. Antiestrogens are drugs that inhibit the effects of estrogen by inhibiting the enzyme aromatase or by blocking estrogen receptor action (226). Similar to SARMs, SERMs have been developed to tissue selectively antagonize estrogen actions (226). Although antiestrogens have been successfully used to treat various diseases and ailments, that is, breast cancer, infertility (40,477), they are taken by athletes to reduce the aromatizing effects from anabolic steroid use. In males, antiestrogens may increase endogenous production of testosterone (226,358), which is why some athletes use them upon completion or near completion of an androgen cycle. Some androgens have minimal aromatizing properties (i.e., Deca-Durabolin) and some are more potent (i.e., Equipoise, Dianabol, Halotestin, testosterone) (495), thereby enticing athletes to use antiestrogens as part of the drug stack. Differential androgenic effects have also been reported among use of different testosterone esters, for example, testosterone enanthate vs. buciclate vs. undecanoate (526). Several undesirable side effects (i.e., gynecomastia, water retention, and other health risks) of androgens use are caused by aromatization into estradiol and other estrogens. Studies show substantial elevations in plasma estradiol concentrations with testosterone or anabolic steroid administration (85,508).

Two categories of antiestrogens include aromatase inhibitors and receptor blockers. Aromatase inhibitors block aromatization, that is, aminoglutethimide (Cytadren), exemestane (Aromasin), testolactone (Teslac), formestane (Lentaron), letrozole (Femara), and anastrozole (Arimidex). Aromasin is thought to be one of, if not the, most effective aromatase inhibitors among athletes (326). Selective estrogen receptor modulators and receptor blockers antagonize estrogen receptors, that is, clomiphene citrate (Clomid), tamoxifen citrate (Nolvadex), raloxifene (Evista), and cyclofenil. Clomid is a popular drug used by male bodybuilders (50–100 $mg \cdot d^{-1}$) and is frequently used for 4–6 weeks upon termination of a steroid cycle. Nolvadex is a popular antiestrogen used by athletes consumed ~10–30 $mg \cdot d^{-1}$. Cytadren is also popular as athletes have reported use of 250–500 $mg \cdot d^{-1}$ (although higher doses may be used for the cortisol-controlling effect), and cyclofenil has been used ~400–600 $mg \cdot d^{-1}$ for ~4–5 weeks after a steroid cycle (326). Aromatase inhibitors, SERMs, and other antiestrogens such as Clomid are prescription drugs banned by sport governing bodies including WADA (537).

Thyroid Drugs. The thyroid gland produces 2 key regulatory metabolic hormones: triiodothyronine (T3) and thyroxine (T4). Thyroid hormones produce a multitude of functions in virtually all cells of the human body including critical functions in the nervous, bone, and muscular systems; metabolism; and energy expenditure (82,528). Thyroid drugs (primarily sodium levothyroxine) are typically used to treat thyroid insufficiency or hypothyroidism (167,530). Thyroid hormones are consumed in synergy with other drugs theoretically to potentiate the anabolic response. Athletes, especially bodybuilders, have used thyroid drugs to potentially enhance the anabolic growth processes and offset some negative metabolic effects associated with kilocalorie restriction. Some thyroid drugs used by athletes include Cytomel, Triacana, and Synthroid in supraclinical doses (326). Unsupervised use of thyroid drugs can disrupt the hypothalamic-pituitary-thyroid axis and produce negative side effects such as bone and skeletal muscle catabolism, heart palpitations, agitation, shortness of breath, irregular heartbeat, sweating, nausea, irritability, tremors, restlessness, and headaches (113,167). Thyroid drugs are prescription pharmaceuticals used for medicinal purposes and unethical when used to enhance athletic performance. There is a paucity of research examining potential ergogenic effects of thyroid drugs on athletic performance. Thus, their utility is unclear and use is contraindicated.

Central Nervous System Stimulants. Stimulants increase central nervous system activity and increase mental acuity, alertness, physical energy, thermogenesis, and exercise performance, for example, muscle strength, endurance, improved reaction

time, and weight loss (27,449). However, side effects such as nervousness, anxiety, heart palpations, headaches, nausea, cardiomyopathy, high blood pressure, and in some rare cases a stroke may occur. Stimulants include amphetamines, caffeine, cocaine, and ephedrine. Many stimulants are banned substances but still are commonly used by athletes (537). Caffeine, pseudoephedrine, synephrine, and both ephedrine and methylephedrine (in concentrations $<10\ \mu g \cdot mL^{-1}$) are not prohibited. Amphetamines release stores of norepinephrine, serotonin, and dopamine from nerve endings and prevent reuptake that leads to increased amounts of dopamine and norepinephrine in synaptic clefts (27). The sympathetic response is greatly enhanced by greater neurotransmitter availability. The American Medical Association in conjunction with the NCAA began investigating alleged widespread use of amphetamines by athletes in 1957 (283). Bents et al. (52) showed that 7–16% of collegiate hockey players reported some past and present use of amphetamines. Ingested amphetamines are absorbed from the small intestine and peak blood concentrations occur 1–2 hours after use (27). Stimulant effects may be seen with 10–40 minutes after consumption and may last up to 6 hours. Amphetamine metabolites are excreted in the urine where they can be detected (up to 4 days after use) via drug testing.

Ephedra has been used to treat respiratory problems and is commonly present in pharmaceuticals such as bronchodilators, antihistamines, decongestants, and weight loss products. Ephedrine use is banned by the NCAA. Because ephedrine alkaloids are found in common cold medicines, American collegiate athletes need to be aware that consumption of these products can result in a failed drug test especially because some products contain higher quantities of ephedrine alkaloids than what is reported on the label (504). Chester et al. (107) showed that use of over-the-counter decongestants containing phenylpropanolamine and pseudoephedrine for 36 hours resulted in peak drug urine concentrations 4 hours after the last dose with elevations persisting up to 16 hours after. The incidence of ephedrine use has been shown to be high in bodybuilders (504), weightlifters (218), and gym members (280).

Performance changes with ephedrine use are less clear. Initial use of pseudoephedrine did not enhance running or cycling performance (108,110,202,489), although one study found greater peak power during cycling and muscle strength (201). Studies examining ephedrine supplementation alone have only shown limited ergogenic effects on performance (50,256). However, a caffeine/ephedrine stack can result in higher blood pressure, heart rate, blood glucose, minute ventilation, insulin, free fatty acids, and lactate concentrations during exercise (50,224) and result in greater increases in power output, time to exhaustion (50,51), and faster 3.2 km loaded run times (49).

Clenbuterol. Clenbuterol (i.e., Spiropent, Prontovent, Novegam, Clenasma, Broncoterol) is a β2 agonist used to treat asthma because it is a bronchodilator and has similar hormonal, metabolic, cardiovascular, and sympathetic nervous system effects as stimulants. Clenbuterol is banned in competition by WADA. However, athletes have used clenbuterol because (a) it has been shown to increase muscle hypertrophy and strength (more so than other β2 agonists) and (b) it increases lipolysis (99,158,277,471). Clenbuterol has been shown to enhance muscle strength and power (409) and is usually stacked with other drugs. It has been used in an "on/off" manner such that athletes will use for 2–3 weeks and then discontinue use for 2–3 weeks at doses of ~60–140 $mcg \cdot d^{-1}$ (326). The half-life of clenbuterol is ~35 hours and it accumulates with subsequent repeated doses. Approximately 97% of clenbuterol is removed from the body within 8 days (334). Side effects of clenbuterol use include increased heart rate, heart's force of contraction, tremors, muscle cramps, palpitations, insomnia, nervousness, and headaches (294).

Human Chorionic Gonadotropin (hCG). Human chorion ganadotropin is a dimeric glycoprotein hormone found in the placenta of women (226). Athletes use hCG because it has been shown to stimulate the Leydig cells to produce testosterone naturally (226). In men, hCG acts very similar to LH, as it has specific target receptors on Leydig cells, activation leads to activation of a cyclic adenosine monophosphate secondary messenger system, and stimulates steroidogenesis (292). It has been shown that 3,000 IU of hCG resulted in significant elevations in testosterone in athletes (264). A 50% elevation in plasma testosterone level was observed 2 hours after injection of 6,000 IU of hCG (430). The response appears biphasic in that peak elevations in plasma testosterone may be observed 3–4 days after hCG administration (292). About 20–30% of hCG administered is excreted in urine within 6 days (292). Often hCG is stacked with androgens when athletes are cycling down in an attempt to enable athletes to rejuvenate their own testicular size and testosterone-producing capacity and to maintain some of the anabolic effects associated with androgens. Despite acute elevations in testosterone after 1 injection of hCG in androgen users just coming off of a cycle (346), it appears administration of hCG (5,000 IU) 3 times per week for a few weeks may be needed to maintain normal testosterone concentrations (347). In addition, use of hCG to increase natural testosterone production has been used to stabilize the T:E ratio (as epitestosterone increases) for athletes doping with testosterone (292). Kicman et al. (291) and Cowan et al. (123) have shown that a single-dose hCG administration (5,000 IU) resulted in substantial elevations in testosterone, yet no significant change in the T:E ratio. Because hCG increases testosterone, several side effects with testosterone or anabolic steroid use may also be seen with hCG, especially at higher doses. Doses of 1,000–7,000 IU of hCG injected every 5 days have been used by athletes in 3–4 week cycles, although others have used greater quantities for cycles extending beyond 8 weeks (326).

Site Enhancement Drugs. Site enhancement drugs are mostly used by bodybuilders. These drugs, for example, Synthol, Nolotil, Caverject, cause temporary muscle size increase when injected locally (326). A drug formerly used, Esiclene, was used as well because it led to swelling and inflammation when injected locally. However, other drugs are now used by bodybuilders for local site enhancement. Synthol is composed of medium-chain triglycerides, lidocaine, and benzyl alcohol and is injected intramuscularly where it lodges between the fascicles. Repeated injections lead to greater volume within the muscles. Bodybuilders have been suggested to inject 1–3 mL every day or every other day for 2–3 weeks (326). Scientifically, little is known about these drugs and potential side effects currently. Use of these drugs is unethical and could lead to potential serious side effects.

Frequency of Androgen Use

The scientific evidence concerning the prevalence of the nonmedical use of androgens within the U.S.A. is sorely lacking. A recent report has indicated that since 1993 the lifetime use of androgens for nonmedical reasons has remained at a consistent 1% in the college student population (348). Considering that there are more than 40 million college graduates in this country (369), it can be crudely extrapolated that more than 400,000 college graduates have used androgens during their lifetime. In addition, a recent survey has suggested that nearly half of all users of androgens hold a college degree (114). Considering then that half do not, it may be further extrapolated that more than 800,000 individuals in the U.S.A. have used androgens during their lifetime. However, most surveys examining the nonmedical use of androgens have focused on collegiate and adolescent students and athletes. Information concerning adult use is generally limited to surveys of individuals who are self-administering androgens.

In the adult population of androgen users, the median age of individuals using androgens is 29 years, with nearly half of them holding at least a bachelors degree and more than 5% of self-admitted users holding a terminal degree (e.g., JD, MD or PhD) (114). Most adult users of androgens in the U.S.A. are whites (88.5%) and employed as professionals with yearly income exceeding that of the general population (114). The primary reason for drug use among the general population of androgen users appears to be related to increases in strength and muscle mass and wanting to "look good" (114,246). Other motivating reasons for drug use also include reduction of body fat, improvement to mood, and attraction of sexual partners. Interestingly, of the 1,955 androgen-using males surveyed bodybuilding and sports performance were either not motivation for androgen use or of little importance (114). Although recent media reports have focused on performance-enhancing drug use in professional athletes and youth, the majority of adults who self-administer androgens for nonmedical purposes appear to be intelligent, economically stable, white men who are not competitive athletes.

Based on media exposure, the underlying belief is that the use of performance-enhancing drugs, specifically anabolic steroids and GH, is rampant among professional athletes today. Although 67% of the U.S. powerlifting team in 1995 was reported to have used anabolic steroids (520) and anecdotal reports suggested that anabolic steroid use in the NFL ranged between 50 and 90% of players during the 1970s and 1980s (543), the available scientific evidence of the past few years indicate that illegal performance-enhancing drug use among competitive athletes is declining. In a survey of almost 14,000 NCAA student athletes, the NCAA reported that the number of collegiate athletes who self-admitted to androgen use has declined over the past 12 years (14,368). According to the survey, the number of collegiate athletes who self-admitted to androgen use has decreased from 4.9% in 1989 to 1.4% in 2001. These trends were apparent in all sports including football, in which androgen use among those athletes was reduced by approximately 50% during this same period (14,368). Interestingly, the racial/ethnic differences reported among the general population of androgen users appear to become more balanced among collegiate athletes. Androgen use among African-American collegiate athletes (1.1%) appears to be as common as that seen in white student athletes (1.1%) (213). Regardless, specific use patterns among professional and Olympic caliber athletes remain a mystery and unfortunately professional sport organizations within the U.S.A. do not release any of their drug testing results to the general public. Consequently, most information emanating from professional sports has been based on innuendo and hearsay.

A concern that first appeared on NCAA performance-enhancing drug surveys was the change in the age of initial androgen use among collegiate athletes who self-admitted to using these drugs. During the initial years of the survey, the majority of college athletes using these banned drugs did so toward the end of their college careers. Presumably, this was to enhance their chances of playing at the next level (i.e., professional sports); however, the trend seen in recent publications of the survey began to show a decrease in the age of initial androgen use. It appears that more than 40% of college athletes who admit to using androgens today appear to first begin using these drugs in high school (368). Even more disturbing were reports that androgens use was also beginning to be seen in middle school students (175,478). However, a recent study was unable to support these findings (246).

Examination of androgens use among the adolescent population appears to be following the same trend seen in the professional and collegiate athlete. Early studies examining performance-enhancing drug use in adolescents reported that androgen use at the secondary level ranged from 6% (91) to 11% in males (274). During the past 10–15 years, the use of androgens among adolescents appears to also be on the decline with self-reported use ranging from 1.6 to 5.4% (154,159,246,253,370,441,493). Studies showing a higher incidence (>6% self-admitting) of use have specifically

examined high school football players (478). However, comparisons of androgen use among adolescent athletes and nonathletes have been inconclusive. Although some studies have indicated that there is no difference in androgen use among adolescent athletes and nonathletes (154,370), others have suggested that athletes tend to use these drugs with greater frequency than nonathletes (441,493). The pattern of performance-enhancing drug use among adolescents does appear to increase as students move through high school, with a recent study indicating that 6% of high school male twelfth graders admitted to using androgens (246). In addition, androgen use among adolescents may be more prevalent in the south (3.46%) vs. adolescents living in the Midwest (3.0%), west (2.02%), or northeast (1.71%) (159). In contrast to adults who self-administer androgens, adolescents who use these drugs appear to have below-average academic performance and are more apt to use recreational drugs (159,359). Interestingly, recent research has suggested that substance use, fighting, and sexual risk are better predictors of adolescent androgen use than participation in competitive sports (359).

One of the biggest changes in androgen use patterns has become the prevalence seen in female athletes and adolescents. Males have generally been reported to have a 3- to 4-fold greater prevalence in androgen use than females, with frequency of use patterns in females varying between 1.2 and 1.7% (159,160). However, in contrast to the declining use reported among male adolescents, the early part of this decade has resulted in several investigators reporting a greater frequency of androgen use in female adolescents that have ranged from 2.0% (359) to 2.9% (253). However, several recent studies have indicated that this trend toward a greater frequency in androgen use among female adolescents may have been overstated or at least declining (154,246).

Results from recent studies do suggest a decline in androgen use among collegiate athletes and adolescent males. However, the earlier onset of initial anabolic steroid use, a potentially greater prevalence in the female population, and the frequency of use in the nonathletic population indicate that the problem of androgens is becoming more societal than segmental regarding specific population groups.

Medical Issues Associated with Androgen Use and Abuse

The surreptitious nature of androgen abuse has rendered it difficult to conduct systematic investigations of the adverse effects of androgens in athletes and recreational bodybuilders. Consequently, these investigations have been sparse and confounded by the enormous variability in the types of drugs used; the dose, frequency, and duration of androgen use; the age at initiation; and concurrent use of accessory drugs. The veracity of self-reported drug use is always suspect.

It is remarkable that the frequency of serious adverse effects associated with androgenic steroid use has been as low as it has been reported; this has abetted the false perception that these drugs are "not too dangerous" and contributed to a sense of complacency among regulatory agencies. Some of this false sense of safety relates to the low frequency of adverse effects observed with substantially lower doses of androgens used in clinical trials than those used by athletes and recreational bodybuilders. Although the highest dose of testosterone enanthate used in clinical trials has been 600 mg weekly, 60% of androgen users in a survey reported using 1,000 mg of testosterone or its equivalent (388). Furthermore, 25% of androgen users also used GH or insulin (388).

Table 5 lists the adverse events that have been reported in association with androgen abuse, including mood and psychiatric disorders (406); increased risk of suicidal or homicidal death (389); deleterious changes in the cardiovascular risk factors, including a marked decrease in plasma HDL cholesterol level (204,391) and changes in clotting factors (15); suppression of the hypothalamic-pituitary-testicular axis and spermatogenesis resulting in infertility; and increase in liver enzymes (144,397,467). Individuals abusing androgens often also concomitantly abuse other accessory drugs, including stimulants, such as amphetamines and cocaine; these accessory drugs may have serious adverse effects of their own. Also, individuals who abuse androgens may engage in high-risk behaviors that may increase the risks of HIV infection, injury, or violence.

Androgen Abuse and Mortality. A number of deaths due to unexpected coronary and cerebrovascular events have been reported among androgen users (351,531), but these reports are largely anecdotal and they do not establish a causative role of androgen use in these deaths. There have been remarkably few systematic investigations of the mortality and health consequences of androgen use by athletes. Parssinen et al. (389) investigated mortality and underlying causes of mortality among 62 powerlifters who had achieved the top 5 positions in weightlifting competitions in the 82.5–125.0 kg weight categories during the 1977–1982 period. The reference group included age-matched individuals from the general population. Thirteen percent of powerlifters and 3% of the age-matched control group died during this period. Suicides, myocardial infarction, hepatic coma. and non–-Hodgkin's lymphoma contributed to deaths among powerlifters. Thus, in this relatively small series, the risk of death among the powerlifters was 4.6 times higher than that in the control population. In another study, the median age of death among androgen users who died and were autopsied was 24.5 years (398); this remarkably young age of death among androgen users is even lower than that for heroin or amphetamine users (398). Another study of patient records in Sweden (399) also reported substantially higher standardized mortality ratios for subjects who were androgen users than for those who were not, indicating increased risk of premature death among androgen users.

Thiblin et al. (498) investigated the cause and manner of death among 34 androgen users whose deaths were investigated medicolegally: 32% committed suicide, 26%

Table 5. Potential adverse effects associated with androgen use.*

Potential adverse effects of high doses of androgens
Behavioral and psychiatric side effects
Increased risk of suicidal and homicidal death
Depression
Hypomania and mania
Increased risk of the use of stimulants and psychoactive drugs, and accessories such as hCG, clomiphene, and aromatase inhibitors
Cardiovascular complications
Lowering of HDL cholesterol
Increased LDL cholesterol
Sudden cardiac death
Myocardial hypertrophy and dysfunction
Prolonged suppression of hypothalamic-pituitary-testicular axis
Hepatic dysfunction, neoplasms, and peliosis hepatic
Gynecomastia
Potential adverse effects of intramuscular injections
Local infection and abscess
Systemic infection, including HIV and hepatitis C virus
Unique adverse effects associated with androgen use in women
Hirsutism
Clitoral enlargement
Change of body habitus, including widening of upper body torso
Breast atrophy
Menstrual irregularity
Unique adverse effects associated with androgen use in children
Premature epiphyseal fusion and growth retardation
Premature virilization in boys and masculinization in girls
Increased risk of unhealthy behaviors
Use of alcohol, tobacco, and other drugs
Less frequent seatbelt use
More sexual activity
Antisocial behavior
Declining academic performance
More fasting, vomiting, diet pill, and laxative use by young girls

*hCG = human chorionic gonadotropin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HIV = human immunodeficiency virus.

were victims of homicide, and 35% of deaths were deemed accidental (498). Use of multiple drugs, cardiac causes, and impulsive and uncontrolled violent behaviors were among the contributory causes of accidental deaths (498).

A majority of androgen users who die prematurely also have used other psychoactive drugs (398). Androgen users who commit suicide have been noted to express depressive or hypomania-like symptoms or to have committed acts of violence or experienced interpersonal difficulties at work or in personal life in the period immediately preceding suicide (499).

Cardiovascular Effects of Androgens. Androgens affect the lipoprotein profile, myocardial mass and function, cardiac remodeling, and the risk of thrombosis (75,143,284,340,351, 372,431,488). Several potential mechanisms have been proposed to explain the adverse cardiovascular effects of androgens (351). High doses of androgens may induce a proatherogenic dyslipidemia and thereby increase the risk of atherosclerosis, increase the risk of thrombosis through their effects on clotting factors and platelets, induce vasospasm through their effects on vascular nitric oxide, or induce myocardial injury because of their direct effects on myocardial cells (180,349,351).

The effects of androgens on plasma lipids and lipoproteins depend on the dose, the route of administration (oral or parenteral), and whether the androgen is aromatizable or not (29,47,58,75,151,255,265,289, 463,464,529,545). Parenteral administration of replacement doses of testosterone is associated with a small decrease in plasma HDL cholesterol levels and little or no effect on total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels (58,463,529), but supraphysiologic doses of testosterone, even when administered parenterally, markedly decrease HDL cholesterol levels (63,456). In contrast, orally administered, 17-alpha-alkylated, nonaromatizable androgens produce greater reductions in plasma HDL cholesterol levels and greater increments in LDL cholesterol than parenterally administered testosterone (265).

Increases in left ventricular mass have been reported among users of androgenic steroids (143,144,284,288,351,392,488). As many androgen users are powerlifters who engage in high-intensity resistance training that can induce left ventricular hypertrophy, it is not clear whether the left ventricular hypertrophy reported in powerlifters is a consequence of resistance training or androgen use or both (392). Although we do not know for sure whether the increase in left ventricular mass observed in androgen users is beneficial or deleterious, a study of left ventricular function in power athletes who were using androgens found significant impairment of both systolic and diastolic function (140,145). In another study, Urhausen et al. (507) used echocardiography to assess left ventricular mass and wall thickness among male powerlifters and bodybuilders who were currently using androgens, ex-users who had not used androgens for more than 12 months, and weightlifters who had never used androgens. Current androgen users had higher left

ventricular muscle mass than nonusers or previous users (507). The E:A ratio (a measure of the peak velocity of the early rapid filling [E-wave] and filling during atrial systole [A-wave]) is reduced in powerlifters using androgens, suggesting altered diastolic function (479). Large doses of androgens may increase the risk of heart failure and fibrosis (143,144,288,351,372,392,488). Myocardial tissue of powerlifters using large doses of androgens is infiltrated with fibrous tissue and fat droplets (372).

There are several case reports of sudden deaths among power athletes who were abusing androgens (143,144,150, 185,186,231,333,488). Many of the sudden deaths have been associated with myocardial infarction. Some of the myocardial infarctions were deemed nonthrombotic, leading to speculation that androgens might induce coronary vasospasm (392). These case reports are largely anecdotal, and a causative relationship between androgen use and the risk of sudden death is far from established. Power athletes using androgens often have short QT intervals but increased QT dispersion in contrast to endurance athletes with similar left ventricular mass who have long QT intervals but do not have increased QT dispersion (479). QT interval dispersion has been used as a noninvasive marker of susceptibility to arrhythmias (411); we do not know whether this predisposes powerlifters who abuse large doses of androgens to ventricular arrhythmias.

Psychiatric and Behavioral Effects of Androgens in Athletes. Anecdotal reports of rage reaction in androgen users, referred to as "roid rage," have attracted a great deal of media attention. However, placebo-controlled trials of testosterone have shown inconsistent changes in anger scores or measures of aggressive behaviors (129,303,407,487,503,541). Several factors may have contributed to this inconsistency of results across trials. The instruments used to measure aggressive behavior have varied across trials, and it is possible that the self-reporting questionnaires did not have sufficient sensitivity to detect small, but significant, changes in aggression. Differences in weight training and related practices; concurrent use of other substances, such as alcohol, psychoactive drugs, and dietary supplements; and preexisting personality or psychiatric disorders are important confounders in interpretation of data related to behavioral effects of androgens (30). None of the controlled trials of testosterone have demonstrated significant change in aggression at physiologic replacement doses of testosterone. In fact, testosterone replacement in healthy androgen-deficient men has been reported to improve positive aspects of mood and attenuate negative aspects of mood (522). It is notable that only a small number of subjects (less than 5%) in controlled trials have demonstrated marked increases in aggression measures, and only with the use of supraphysiologic doses of testosterone, a majority of participants show little or no change (129,303, 407,487,503,543). It is possible that high doses of androgens might provoke rage reactions in a subset of individuals with preexisting psychopathology. Indeed, aggressive individuals–perhaps those with certain personality disorders–may be more prone to abuse androgens. In a survey, more AAS users than controls had worked as doormen or bouncers (357). Among certain groups of criminals, the risk of having been convicted of a weapon offense was higher for androgen users than for nonusers (295). Anecdotal reports suggest that even among individuals without histories of psychiatric disorders or antisocial personality disorder or violence, the use of high doses of androgens might predispose men to violent or homicidal behavior (405).

It is possible that because of strong societal constraints against aggressive behavior, the self-reporting instruments fail to capture changes in the participant's behavior. However, when confronted with a provocative challenge, the individuals receiving high doses of androgens might display unexpectedly high level of aggression and rage. This hypothesis was tested by Kouri et al. (303) using an innovative study design. These investigators reported that administration of supraphysiologic doses (600 mg weekly) of testosterone enanthate to healthy young men was associated with a significant increase in aggressive responses than placebo administration. During the investigation, healthy young men randomly received either placebo or graded doses of testosterone. At baseline and at the end of the treatment period, the participants were asked to play a game against a fictitious opponent; the participants were unaware that the opponent was fictitious. The participants had the choice of pressing button A to receive a financial reward or button B that would take money away from a fictitious opponent (aggressive responding). The objective of the game was to achieve the highest monetary gain and the best strategy to achieve that goal was to keep on pressing button A. Remarkably, individuals receiving supraphysiologic doses (600 mg weekly) of testosterone enanthate opted to select button B (to punish the fictitious opponent) with greater frequency and thus had higher scores on aggressive responding than those associated with no testosterone or lower doses of testosterone. Thus, when provoked by a hostile situation, the level of aggressive response was higher when individuals were receiving high doses of testosterone than when they were receiving placebo or lower doses of testosterone enanthate.

Steroid users experience high frequency of mood disorders, such as mania, hypomania, or major depression, during androgen use (339,406,408,509). Major depression has been reported during periods of androgen use but is more often observed during withdrawal of high-dose androgen use (339,406,509). A high proportion of women athletes using high doses of androgens report symptoms of hypomania and depression, rigid dietary practices, and dissatisfaction and preoccupation with their physique (219).

Kanayama et al. (279) have reported a high frequency of prior androgen abuse among male substance abusers. In a

sample of 223 male substance abusers, who were hospitalized for the treatment of alcohol, cocaine, and opioid dependence, 13% reported prior androgen use, leading those investigators to speculate that AAS use may predispose some individuals to substance abuse.

Liver Toxicity. The elevations of liver enzymes, cholestatic jaundice, hepatic neoplasms, and peliosis hepatis have been reported mostly with the use of oral 17-alpha alkylated androgenic steroids (94,146,301,390,466,467) but not with parenterally administered testosterone or its esters (95). Most cases of hepatic neoplasms in association with androgen use have occurred in patients with myelodysplastic syndromes (366). The risk of hepatic dysfunction during androgen administration probably has probably been overstated (145,247), being extremely uncommon in individuals receiving parenteral androgens. Furthermore, it is not clear whether elevations in aspartate aminotransferase and alanine aminotransferase during androgen administrations are the result of liver dysfunction or of muscle injury resulting from strength training or a direct transcriptional effect of androgens on AST gene (145,397).

The Suppression of Hypothalamic-Pituitary-Testicular Axis. Androgen administration suppresses endogenous pituitary LH and follicle-stimulating hormone (FSH) secretion and indirectly testicular testosterone and sperm production (200,337). Because of predictable suppression of the hypothalamic-pituitary-testicular axis, men using androgens may experience subfertility or infertility (327). Indeed, androgens, alone or in combination with other gonadotropin inhibitors, are being investigated as potential male contraceptives (538).

After discontinuation of the exogenously administered androgen, the recovery of the hypothalamic-pituitary axis may take weeks to months, depending on the dose and duration of prior androgen use (88–90,262). After discontinuation of exogenous androgen use, circulating testosterone concentrations may fall to very low levels as the effects of exogenous testosterone wear off and the endogenous axis has yet not recovered. During this period, the users may experience troublesome symptoms of androgen deficiency, including loss of sexual desire and function, depressed mood, and hot flushes. Some patients who find these withdrawal symptoms difficult to tolerate may revert back to using androgens or may seek recourse to other psychoactive drugs, thus perpetuating the vicious cycle of abuse, withdrawal symptoms, and dependence (88–90). Others may resort to off-label use of aromatase inhibitors or hCG obtained illicitly based on the folklore widely prevalent in the gymnasia that these agents can accelerate the recovery of the hypothalamic-pituitary-testicular axis, although there is no evidence to support this premise. The long-term suppression of the hypothalamic-pituitary-testicular axis with its attendant risk of dependence and continued use of androgenic steroids are serious complications of androgenic steroid use that have not been widely appreciated.

Gynecomastia. Breast tenderness and breast enlargement are frequently associated with the use of aromatizable androgenic steroids (28,81,139,484). The exact prevalence of breast enlargement in androgen users is unknown, but prevalence rates as high as 54% have been reported (28,139,406,484). In a series of 63 patients referred for surgical correction of gynecomastia, 20 men had used anabolic steroids (28). It is not uncommon for athletes to use an aromatase inhibitor or an estrogen antagonist in combination with androgenic steroids to prevent breast enlargement.

Androgen Abuse and Insulin Resistance. The effects of testosterone on insulin sensitivity are biphasic and depend on the dose. In cross-sectional studies, low testosterone levels are associated with increased risk of insulin resistance and type 2 diabetes mellitus (132,164,220,221,402,403). Testosterone replacement in castrated rats and hypogonadal men improves measures of insulin sensitivity (249); however, supraphysiologic doses of testosterone render castrated rats insulin resistant (249). Orally administered 17-alpha alkylated androgens also have been associated with insulin resistance and glucose intolerance (115).

Risks Associated With Intramuscular Injections of Androgens. The majority of androgen users administer androgens by intramuscular route; 13% of those who use intramuscular injections reported unsafe injection practices (388). Self--administration of intramuscular injections increases the risk of infection, muscle abscess, and even sepsis (172). Transmission of HIV infection and hepatitis has been reported among parenteral androgen users, presumably because of needle sharing or the use of improperly sterilized needles and syringes.

Risks Associated With Excessive Muscle Hypertrophy. Excessive muscle hypertrophy without commensurate adaptations in the associated tendons and connective tissues may predispose athletes using androgens to the risk of tendon injury and rupture and unusual stress on joints (173).

Risks Associated With the Use of Accessory Drugs. It has been reported that 90% of androgen users abuse additional drugs (171,388). Almost one-quarter of androgen users also take hGH or insulin (388). Some of these additional drugs of abuse, such as cocaine, amphetamine, and ephedra, may be associated with potentially serious medical complications.

Other Concerns. There are concerns about potential effects of androgens on the risk of prostate disease (57,59,61). The long-term effects of supraphysiologic doses of androgens on the risk of prostate cancer, benign prostatic hypertrophy, and lower urinary tract symptoms are unknown.

Medical Issues Associated With Androgen Use Among Women. Women taking androgens may undergo masculinization and experience hirsutism, deepening of voice, enlargement of clitoris, widening of upper torso, decreased breast size,

menstrual irregularities, and male pattern baldness (141,390). Some of these adverse effects may not be reversible. In addition, epidemiologic studies have reported an association of elevated testosterone concentrations in women with increased risk of insulin resistance and diabetes mellitus (149).

Medical Issues Associated with Androgen Use Among Children and Adolescents. In addition to the adverse effects observed in adults, adolescents may be susceptible to some unique adverse effects of androgens (103,425,514). Pre- or peripubertal boys and girls may undergo premature epiphyseal fusion, which may result in reduced adult height (103,514). Androgen abuse by children is associated with other unhealthy behaviors, such as use of alcohol, tobacco, and other drugs; less frequent seat belt use; more sexual activity; antisocial behavior; declining academic performance; and more fasting, vomiting, diet pill, and laxative use by young girls (514). Boys may undergo premature or more accelerated pubertal changes, whereas girls may experience virilization.

Testing of Androgens

Current Analytical Methods of Detection. Relative to the various analytical method of androgen detection, current detection techniques suffer from an extensive sample pretreatment and thus from low sample throughput. Developing new test methods, which requires the preparation of suitable reference compounds, will allow modern drug testing techniques to be more widely and more effectively utilized. The availability of numerous synthetic steroids and recombinant peptide hormones has made testing an analytical challenge. Recent advances in mass spectrometry have provided an opportunity to decrease detection by utilizing gas chromatography (GC) coupled to high-resolution mass spectrometry (HRMS). A further improvement may be seen with GC-MS/MS and quadrupole ion traps. Electrospray high-performance liquid chromatography (HPLC) coupled to high-resolution MS (HPLC-MS) has also been applied to the detection and confirmation of peptide hormones in urine. The ability to detect subtle differences in oligosaccharide structure may provide a way to detect abuse of recombinant glycoproteins. Simply decreasing detection limits is not enough; new technology also allows development of a foundation on which to base interpretation. Application of HPLC-MS/MS has allowed direct measurement of steroid conjugates in urine (1,2). The relative importance of sulfate, glucuronide, and other conjugates and metabolites of testosterone and epitestosterone can now be assessed (2). A 2-stage procedure, the liquid chromatography-mass spectrometry (LC-MS) technique, will become a much more effective and straightforward testing method, thus offering additional reliability on doping testing.

In light of this, various athletic commissions around the world have begun to analytically detect androgens by way of the steroid glucuronides-liquid chromatography/mass spectrometry. Once androgens have been ingested, the body starts to convert them so that they can be more easily discharged or eliminated as bodily waste matter. The main androgen derivatives found in urine samples are combined with glucuronic acid. Testing for exogenous androgen use is carried out on a sample of an athlete's urine. It is analyzed using a 2-stage LC-MS (2). The components of the urine sample are first separated using liquid chromatography, and then the presence of androgens is detected using mass spectrometry (2). The results can be quantified by comparison with those obtained from a series of standard solutions with known concentrations of androgen glucuronides (133). These androgen derivatives are complex molecules, and because several reaction steps are involved as well as the purity required, their preparation takes a long time and so the substances are expensive. Furthermore, based on recent change in the threshold for androgen detection where the T:E ratio is now at 4:1 rather than 6:1, methods of detection must now employ the capability of greater sensitivity. More recent advances in MS have provided this capability.

High-Resolution Mass Spectrometry for Low-Level Androgen Detection. Accredited laboratories are required to detect certain androgens at levels of 2 $ng \cdot mL^{-1}$ or lower. Detection at such low levels requires HRMS or tandem mass spectrometry (MS/MS), both of which are more sensitive than conventional mass spectrometry. A mass spectrometer bombards a chemical substance with an electron beam to produce charged particles (ions) that are separated and detected based on their mass to charge ratio. By tuning the instrument to characteristic molecular fragments, drugs can be detected sensitively with little interference from other compounds, which produce different fragments. High-resolution mass spectrometry (HRMS) is better able to distinguish between fragments of interest and those arising from other chemical compounds in the urine and allows detection of steroid residues in urine at levels 5–10 times lower than was possible using the conventional technique. In MS/MS, the fragments from the initial ionization are again bombarded and mass analyzed. New purification techniques have also been introduced, which have been developed as a complement to sensitive detection techniques to increase the sensitivity of drug detection. A method using HPLC to prepare clean extracts for most androgens and their metabolites has been developed and validated. This methodology is now in routine use. An instrument capable of performing MS/MS analysis can complement HRMS, in that MS/MS can give a definitive result with some samples that prove difficult to confirm by HRMS. The main advantage of these sensitive techniques is that androgens can be detected for a much longer time after administration; androgen use can now be identified for weeks longer than was possible a few years ago.

Isotope Ratio Mass Spectrometry for Androgen Detection. The usual technique for detection of androgen use is to compare its concentration with that of a related compound, epitestosterone, in the urine (T:E ratio). A T:E ratio greater than 4

may indicate androgen use. However, there is a wide variation in natural T:E ratios between individuals, so that in some cases the T:E ratio may be above 6 even though the individual has not taken androgens, whereas in others the value may stay below 4 despite androgen use. The natural T:E ratio, measured over a period, tends to be constant, and any variation in an individual's T:E ratio over time may indicate androgen use. One technique that can complement the measurement of T:E ratios is the use of GC coupled to IRMS (GC-IRMS). This technique utilizes the fact that natural and administered substances, such as testosterone, have small but measurable differences in the ratio of carbon-12 to carbon-13 isotopes (C12:C13 ratio) (because of the different pathways used in the preparation of the natural and synthetic forms). By measuring the C12:C13 ratio of androgens detected in urine, GC-IRMS can distinguish exogenously administered androgens (synthetic form) from endogenously synthesized androgens (natural form). This provides an ability to identify androgen abuse in cases that would have previously gone undetected. The application of this technique is not simple because the instrumentation is expensive and requires high precision, and larger sample sizes are needed, which increases the amount of sample preparation required before analysis.

Criteria for Detection. The primary biological fluid used for detecting androgen use has typically been urine. Urinary analysis has been successful for the majority of androgens, especially the synthetic varieties that have specific structures easily identifiable by GC-MS. However, the detection of androgens is not absolute and does involve limitations. Methods for detecting the use of androgens depend on alterations in the normal urinary testosterone (T) level. Much work has been done with the intent of determining appropriate urinary markers indicative of androgen use. Traditionally, the ratio of androgen glucuronides to epitestosterone (E; 17-α-hydroxy-4-androstene-3-one) has been used, as was adopted by the Medical Commission of the IOC, with a cutoff point of ≥6 being the primary indicator of androgen self-administration (386) compared with the normal urinary T:E ratio for healthy athletes not using androgens being approximately 1 (293). The increase of the T:E ratio after high-dose androgen use results from increased T excretion and a subsequent decrease in E output (134). Even so, however, some athletes have produced false--positive results revealing T:E ratios ≥ 6 with subsequent verification that no androgens had been administered (133). It has been suggested that this problem could be attenuated by taking into account the sulfate excretions of epitestosterone in the T:E ratio, thereby suggesting that the relevant threshold of the T:E ratio being 3 would be a more sensitive maker of covert androgen use (134).

World Anti-Doping Agency defines as suspect a T:E ratio of 4:1. This is more than 6 *SD*s for the expected norm of 1:1 in the general population. Using a smaller ratio, however, would be impractical. For example, using publicly available data, only 3 of nearly 500 cases since 2004 where the T:E ratio was between 4:1 and 6:1 resulted in a confirmed adverse analytical finding under the WADA system. The preliminary GC/MS screen for testosterone in urine is known as the T:E ratio test. T stands for testosterone; E, epitestosterone, a natural, inactive isomer of testosterone. In most individuals, the T:E ratio is ~1:1. A T:E ratio of 4:1 may indicate the presence of synthetic testosterone. World Anti-Doping Agency has established that a T:E ratio of ≥4:1 is the threshold that triggers further testing of an athlete's sample. Upon collection, each sample from an athlete is split into 2 vials, A and B, and sample A is tested first. The T:E test has 2 parts: a screening phase and a confirmation phase. T and E are identified by the main MS fragment ions produced from their respective trimethylsilyl derivatives in the screening phase. Once a chromatogram is produced, the T:E ratio is estimated on the basis of the peak area ratio. If the T:E ratio is ≥4:1, then a GC/MS confirmation test is performed. Two new aliquots, one that is hydrolyzed and one that is not, are prepared for this test. The aliquot without hydrolysis measures free T and E to verify that the urine sample did not break down.

Interestingly, because the secretion of testosterone is under the control of LH, it has been suggested that the urinary T:LH ratio could conceivably be a useful marker for detecting androgen use (87). High-dose androgen use is known to result in dose-dependent suppression of both serum and urinary LH (291), based on the premise that LH excretion is typically reduced to a lesser extent than the decrease in both epitestosterone and testosterone conjugates. Therefore, increased serum and urinary T:LH ratios in the presence of a normal T:E ratio may be indicative of androgen use. In light of this, it has been shown that a urinary T:LH ratio of ≥30 is a more sensitive marker of androgen use than the urinary T:E ratio of ≥6, and remains sensitive for twice as long as urinary T:E (396).

Effect of Genotype on Testing Results. Doping tests for the past 10 years have demonstrated that Asian individuals excrete a reduced amount of testosterone glucuronide (136,387), which may result in an increased risk of a false-negative drug test in this ethnic group. This was part of the motivation for changing the upper normal limit of 6 to 4 for the T:E ratio. Recent studies have suggested that a deletion polymorphism in the gene coding for uridine diphospho-glucuronyl transferase 2B17 (UGT2B17), the principle enzyme for the glucuronidation of androgens and their metabolites, is associated with a T:E ratio below 0.4 (259). This was seen to be more common in Asian than in a white population.

A recent study by Schulze et al. (440) examined 55 male subjects who were genotyped for the UGT2B17 deletion. Of these subjects, 31% were homozygous for the gene deletion, 44% were heterozygous for the gene deletion, and 25% had 2 copies of the gene. Subjects had originated from different ethnicities. After a single injection of 500 mg of testosterone enanthate, urine samples were collected for 15 days. Results demonstrated that the rate of increase in testosterone

glucuronide excretion was highly dependent on the genotype of UGT2B17. Forty percent of the subjects who were homozygous for the gene deletion never reached the T:E cutoff of 4 during the 15 days of the study. Interestingly, in the group that had both copies of the gene, 14% of the individuals had baseline T:E ratios above 4, resulting in a false-positive test. However, by changing the ratio to 1.0 in the homozygous group and to 6.0 in the group that had both copies of the gene, the sensitivity of the test increases to 100% within 6 days from injection. Thus consideration of the genetic variation of testosterone glucuronidation enzymes appears to be important in developing appropriate doping tests.

Legal Issues Associated With Androgens

Although androgens have always required a physician's prescription for use, it was not always listed as a controlled substance. However, as a result of mounting pressure related to androgen use among American adolescents, the U.S. Congress in 1990 amended the controlled substances act to include androgens. This was known as the Anabolic Steroid Control Act. The passing of this law reclassified androgens as a schedule III substance. The impact of this was to make it a crime to use these drugs for nonmedical purposes. Other schedule III substances include weak opioids such as codeine and Vicodin, barbiturates, amphetamines, and methamphetamines. By 2004, an amended version of the Anabolic Steroid Control Act was passed that modified the definition of androgens to include 26 additional compounds that comprised designer androgens, such as THG, and prohormones, such as androstenedione.

The simple possession of any schedule III substance including androgens is punishable by up to a year in prison and/or a fine of $1,000. However, if the person who is caught in possession of androgens has a previous conviction for drug possession or another crime they will be imprisoned for at least 15 days and up to 2 years with a minimum fine of $2,500. A third conviction for possession will require imprisonment for at least 90 days but not more than 3 years with a minimum fine of $5,000. Selling anabolic steroids or possessing androgens with intent to sell is a federal felony offense. First conviction is punishable by up to 5 years in prison and/or a $250,000 fine. A second conviction for distribution of androgens may result in a prison sentence of up to 10 years with fines not exceeding $500,000.

Conviction of androgen possession or distribution results in not only potential prison time and/or fine but may also jeopardize future employment opportunities. If the convicted person holds a license for employment, such as medical and allied health professionals, a conviction may result in a loss of licensure. In addition, students convicted of possession or distribution of schedule III substances may forfeit their rights to financial aid and other benefits. Clearly, users of illegal performance-enhancing drugs face significant risk for jail time, fines, and jeopardize both present and future employment opportunities.

Direction of Future Research

The efficacy of androgen treatment in muscle wasting diseases has clearly been established. Continued research is needed to further identify clinical populations that may benefit from androgen therapy and combined exercise and androgen treatments. In addition, identification of dosing-related adverse events will provide a clearer understanding of risk vs. reward regarding androgen treatment. Research on selective AR modulation is very promising in this regard and needs to be further elucidated.

Regarding androgen use in healthy athletic populations, there is a need to increase research on maximizing performance gains through modulations in nutritional and exercise regimens and when appropriate the inclusion of legal and efficacious supplements. Providing viable alternatives to athletes contemplating illegal drug use could potentially reduce the number of athletes who are willing to take such chances. In addition, further understanding of the effect of changes in androgen profiles in athletes during the competitive season is warranted. Although anabolic and catabolic hormonal changes have been well documented during various exercise stresses, there are only limited data available concerning changes in competitive athletes during a season of training and competition. Furthermore, investigations designed to study the effect of various recovery methods, nutritional interventions, sport supplements, and exercise routines on endocrine function in such athletes would provide valuable information to coaches and athletes regarding potential methods used to promote an optimal training environment and maximize athletic performance.

Growth Hormone

The purpose of this overview of GH is presented for the most part beyond what is found in classical endocrine textbook aspect of GH physiology. It is vital to gain an understanding of what lies beyond the typical physiology and is related to the use of GH for physical development and enhancement of sport performance.

What Is Growth Hormone?

Growth hormone also called somatotropin in the older literature is a pleiotropic peptide hormone synthesized, stored, and released from the anterior pituitary gland (353). The most commonly measured form of GH is the 191 amino acid isoform. This 22-kDa isoform contains numerous cleavage sites and can be structurally distinguished via its positioning of cysteine residues that are responsible for its internal disulfide loop and smaller disulfide loop located at the C-terminus. Other variants include a 20-kDa form produced by the gene deletion for 14 amino acids and many other post-translational isoforms of unknown physiological significance (42). The GH produced for commercial use is 100% the 22-kDa isoform. This is important information for the detection of hGH abuse.

At present, detection of hGH abuse has not been validated, and this provides the primary motivation for use by athletes. In addition, the measurement and elucidation of its biological properties are complex, as hGH does not exist as a single, molecular species. It has been suggested that more than 100 different hGH isoforms exist, all arising from one of 2 genes (41,43). Post-translational modifications include acetylation, deamination, and hetero- and homo-oligomerization (43,320). The ability to form oligomers via either non-covalent or peptide (cystine) bonds may serve to increase the half-life of the peptide in circulation or may have undiscovered biological properties, such as competitive binding to the GH receptor. Dimeric hGH appears to be the most abundant of the post-translationally modified products, although oligomers up to pentameric GH have been reported. Homo- and hetero-oligomers have been described for the 22- and 20-kDa isoforms. Of particular interest is that small proteolytic fragments and large aggregates are also formed (43). The variable nature of these GH isoforms exists in circulation and encompasses a wide range of molecular weights (42). Thus, understanding the impact of ergogenic use of GH as an anabolic agent is likely complex.

Mediation of GH effects occurs with its interaction with the GH receptor. The GH receptor is a 70-kDa class I cytokine/hemapoietin superfamily protein (319). It is composed of 2 complexes that interact with the GH ligand in a sequential manner to dimerize. Intracellular signaling then occurs through a phosphorylation cascade via the JAK/STAT pathway. The GH receptor exists in abundance in many tissues, including the liver, muscle, and adipose tissue. However, the GH receptor may not be specific to all the GH variants (208,251). For instance, the tibial line receptors, used in a bioassay, do not seem to interact strongly with the 22-kDa monomer (208,251).

What Is the Physiological Role of Growth Hormone?

Its physiological role is linear growth in children, to promote anabolic (tissue building) metabolism, and to alter body composition as part of this anabolic role. Growth hormone actions include the hepatic and local synthesis and release of its main mediator, IGF-1. Its growth-promoting effects include longitudinal bone growth by actions at the epiphysis and the differentiation of the osteoblasts (420). It shares some of these roles with IGF-1, meaning that the direct effect of GH and/or local production of IGF-1 are both required for optimal linear growth.

The release of GH is stimulated by growth hormone–releasing hormone (GHRH) and is inhibited by somatostatin, both hypothalamic hormones. However, there are many other factors that affect GH regulation, most of which use these hypothalamic hormones as a common path. Stimuli to GH release include deep sleep; exercise; stress including heat; hypoglycemia; nutritional intake; some amino acids (see below); some pharmacologic agents, including clonidine, L-DOPA, estrogens, and androgens (through an estrogen-dependent mechanism, especially in adolescents). Inhibitory influences include obesity, ingesting a carbohydrate-rich diet, and several pharmacologic agents, for example, beta-2 adrenergic agonists. The release of GH from the anterior pituitary is pulsatile, meaning that its release is not constant but occurs in bursts (236,251) The largest peak GH secretion occurs about an hour after the onset of sleep, with subsequent smaller peaks occurring during the rest of the sleep period (374).

Its major metabolic effects can be deduced from the alterations in GH-deficient subjects–the reduction of lean body mass, an increase in body fat, and a reduction in bone mineral density. Administering hGH may reverse many of these alterations (see below); however, it is not quite so simple in that hGH has different acute effects depending on the time after natural secretion or exogenous administration. It is insulin-like in the first minutes, but then becomes diabetogenic (anti-insulin) at the liver and at peripheral sites several hours after administration. Glucose utilization is decreased, lipolysis is increased, and the tissues are refractory to the acute insulin-like effects for several hours. Its direct actions include amino acid transport in muscle leading to protein synthesis and an increase in nitrogen balance, increased fat mobilization through lipolysis (increased triglyceride hydrolysis to free fatty acids and glycerol and reduction in fatty acid re-esterification), and an augmentation of lipid oxidation. Clinically these effects can be noted in the longer term by a decrease in body fat and a decrease in the adipopcyte size and lipid content.

The outcome of GH therapy in GH-deficient adults may be an increase in FFM, both body cell mass (muscle), total body water, especially the extracellular compartment, and a decrease in body fat with redistribution from central to peripheral stores (242).

Growth hormone has numerous functions in the organism, including growth and development, metabolism, bone health, hydration status, and cardiovascular function. The diverse multitude of functions would appear to imply that more than one form of GH (i.e., molecular variants) may be necessary to mediate all these functions. However, for the purposes of this review, the focus will be on the effects of hGH on protein synthesis in muscle, as heavy resistance training is primarily focused on this target tissue for development. In fact, understanding the interactions of hGH with other anabolic hormone signals is vital because it is unlikely that athletes use hGH alone. As noted previously, it is likely that GH and anabolic steroids are taken concurrently. Figure 6 depicts the role of GH signaling in response to resistance exercise and also the associated influence of other anabolic hormones, which are commonly associated with anabolic drug use.

The effect of hGH on muscle hypertrophy appears to lie in its ability to indirectly stimulate the mammalian target of rapomyosin (mTOR) pathway via dimerization with its receptor and subsequently activating the phosphorylation cascade of the JAK/STAT pathway. The mTOR pathway

has direct control over several components of translation in protein synthesis via its downstream effectors, ribosomal S6 kinase 1 (S6K), eukaryotic initiation factor-I 4E binding protein-1 (eIF 4E-IGFBP-1), and elongation factor 2 kinase (eEF2) (198,232,338).

Hayashi and Proud (232) reported that GH also stimulates dephosphorylation of eEF2 and activates S6K, thus playing a role in translation, initiation, and elongation of the proteins synthesized. These downstream effects are thought to be a result of the GH-mediated stimulation of phosphatidylinositol 3-kinase and protein kinase B (PKB, also called AKT) (232).

The mTOR pathway can also be activated by the extracellular ligand–regulated kinase (ERK) pathway via phosphorylation of the JAK/STAT pathway subsequent to GH ligand binding to the GH receptor in disease states such as cancer and likely occurs during musculoskeletal protein synthesis (19,335,426) A further role of GH in skeletal muscle growth is related to its ability to increase myonuclear number and to facilitate the fusion of myoblasts with myotubes (469).

It has also been reported that hGH has stimulating role in the incorporation of ingested amino acids on protein synthesis, probably occurring through decreasing leucine oxidation and increasing lipolysis. Growth hormone also potentially blunts insulin proteolytic action and increases free fatty acid availability, both of which may have a sparing effect on the amino acid pool.

However, the most potent anabolic effects of hGH may be related to its role in amino acid metabolism. In a study of exogenous GH infusion, Copeland and Nair (121) reported that an acute local infusion of hGH in healthy men immediately inhibited whole body leucine oxidation

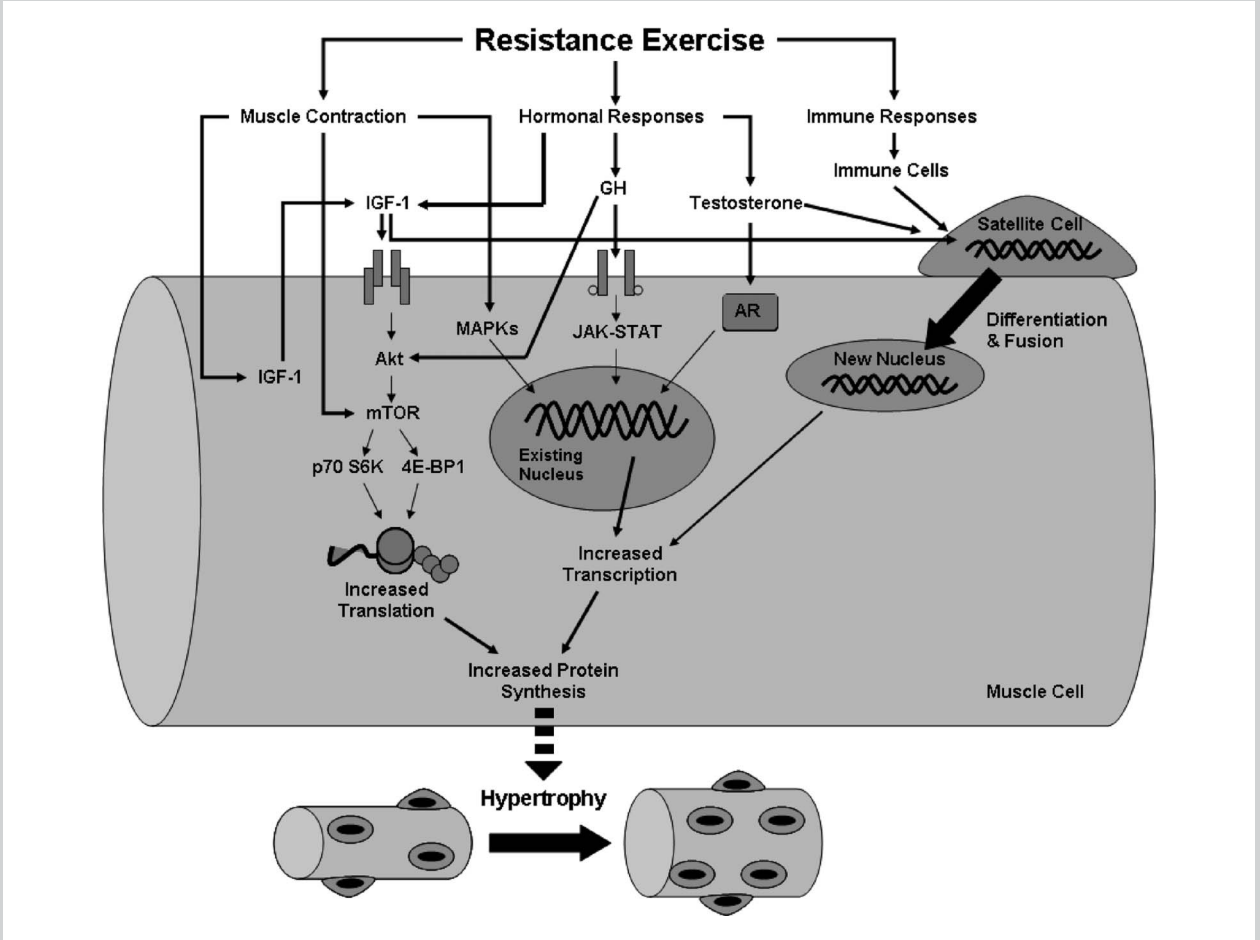


Figure 6. Summary of the signaling responses to resistance exercise. Resistance exercise stimulates muscle fiber contraction and invokes endocrine and immune responses that subsequently activate satellite cells. These various signals stimulate transcription and translation and, over time, muscle hypertrophy. Corresponding increases in satellite cell–derived myonuclei accompany fiber hypertrophy. Akt = protein kinase B; AR = androgen receptor; GH = growth hormone; IGF-1 = insulin-like growth factor-1; JAK = Janus kinase; MAPKs = mitogen-activated protein kinases; mTOR = mammalian target of rapamycin; PI-3K = phosphatidylinositol-3-kinase; p70 S6K = 70-kDa ribosomal protein S6 kinase; 4E-BP1 = eukaryotic initiation factor 4E binding protein-1. Adapted from Spiering et al. (470).

independent of other hormones. In contrast to this finding, others have reported that local skeletal muscle protein uptake occurred in response to local hGH infusion in the forearm, but total body protein metabolism was not affected (197). Furthermore, it appears that uptake by local contractile muscle also occurs, with differences in arteriovenous concentrations reported in at least one exercise study (79). However, the independent effects of GH on amino acid metabolism remain controversial, as other GH-mediated hormones such as IGF-1 may also play a significant role (362).

History of the Use of Human Growth Hormone as an Ergogenic Aid in Athletes

Human growth hormone was first prepared in the 1940s and in such small amounts that there was likely virtually none available for athletic performance (321). It is only the human (and monkey) pituitary GH that has efficacy in man and thus none of the other species' GH can be used (297). With the synthesis of recombinant hGH (rhGH) in the 1980s, a virtually unlimited supply became available, and clinical studies were undertaken in children and adolescents with subnormal growth and adults with GH deficiency, aging, and for performance or aesthetic purposes (see below). The evidence for rhGH to produce salutary ergogenic and performance effects *among athletes* is neither robust nor clear (324,539).

What Is the Clinical Role of Growth Hormone?

Growth hormone is administered to promote linear growth in short children. The following are the Food and Drug Administration (FDA)–approved indications for GH:

- GH deficiency
- CKD
- Turner syndrome
- Small-for-gestational-age infants who fail to catch-up to the normal growth percentiles
- Prader-Willi syndrome
- Idiopathic short stature
- *SHOX* gene haploinsufficiency
- Noonan syndrome

The most common efficacy outcome in infants, children, and adolescents is an increase in linear growth, although it prevents hypoglycemia in some infants with congenital hypopituitarism.

Growth hormone is administered to promote physiologic and psychological well-being and altered body composition in adults with GH deficiency, muscle wasting due to HIV/AIDS, and short bowel syndrome. All other use is "off-label" and has become of intense interest in the sporting world, especially earlier this year with the Congressional hearings related to Major League Baseball.

What Types of Clinical Research Are Being Done With GH?

Clinical research with GH in children is mainly about promoting growth in various pathological conditions, which may stunt growth. In some syndromes, for example, the Prader-Willi syndrome, the alterations in body composition (lean body mass, fat mass, and especially the regional distribution of body fat) are being investigated.

For the adult, the bulk of GH research involves the study of 2 opposite conditions:

1. Growth hormone deficiency to note the changes in well-being, body composition as noted above, and the psychosocial issues of well-being because the major indication for GH treatment in GH-deficient adults is to favorably alter the sense of health-related well-being (244).
2. Growth hormone excess (acromegaly) to note the changes in body composition and health-related well-being, but especially the alteration of cardiovascular risk factors noted with diminishing the GH values by surgery, radiotherapy, and pharmacologic agents (93).

GH Abuse

Growth hormone is listed under class S2 of hormones and related substances in terms of the 2006 prohibited list. Other peptides in this category include EPO and corticotrophin (ACTH) in addition to IGF-1 and insulin. Growth hormone is likely being abused at increasingly prevalent rates, but before describing some of the data, it should be noted that much of what is purported to be hGH, especially on the Internet is not. Of course, any drug taken orally cannot be hGH. Many of the products advertised on the Internet and in magazines are hGH releasers–mainly amino acids and rarely, analogues of hGH-releasing hormone (435). The notion that amino acids release hGH is on solid scientific ground, given that tests for GH sufficiency may include arginine or the closely related amino acid, ornithine. What is not stated is that very concentrated solutions of these amino acids are administered intravenously before GH is released. Also not prominent (note that these are dietary supplements and not subject to FDA oversight) is the physiologic concept of the absolute and then relative refractory period after GH release, irrespective of the cause.

There are many reports that note an increasing prevalence of hGH abuse. These come (mainly) from anecdotal reports including "information" of benefits, from the Internet, a very favorable write-up in *The Underground Steroid Handbook*, and an increasing number of seizures from elite athletes including cyclists and swimmers. What is it that athletes wish to obtain from administering hGH? The athletes wish improved performance, but such studies are difficult to do, either as "clinical trials" or observational studies in athletes; for they rarely take agents singularly but often a "cocktail" of dietary supplements and 1 or more doping agents. Although hGH has not been shown to unequivocally increase muscle strength or to improve performance (324), it is considered one of the drugs of choice because it is extremely difficult to prove that one is receiving it (more about the "window of detectability" later). The structure of rhGH is identical to that of the main isoform of natural hGH; it is secreted in pulsatile manner, meaning that its levels fluctuate widely, from undetectable to clearly in the "doping" range with

a short half-life in the circulation. Exercise is potent stimulus to hGH release, and release may be modified by variations in nutrition and legitimate nutritional supplements, as noted previously.

Liu et al. (324) have systematically reviewed the effects of hGH on athletic performance. Using proper and stringent criteria for a meta-analysis, they reviewed 7,599 titles from the largest databases, reviewed 252 abstracts in detail, and retrieved 56 articles for full-text evaluation. Following their review, just 44 articles representing only 27 *unique* studies met the strict inclusion criteria. The majority of the 303 participants received hGH for an average of 20 days, with a number having received hGH for only 1 injection. They were mainly young men (average age 27 years) and were recreational *not* elite athletes. The average dose was 36 $\mu g \cdot kg^{-1} \cdot day^{-1}$, approximately 5- to 10-fold the therapeutic dose in adults with GH deficiency.

Lean body mass increased in the hGH-treated groups compared with those not treated [2.1 kg (95% CI, 1.3 to 2.9 kg)], with a small but not statistically significant decrease in fat mass (−0.9 kg [CI −1.8 to −0.0 kg]). Body weight did not change significantly. Only 2 studies appropriately evaluated change in strength (142,550). These were the longest trials of 42 and 84 days. On 1RM voluntary strength testing, those receiving hGH showed no change in biceps strength (−0.2 kg [CI −1.5 to 1.1 kg]) or quadriceps strength (−0.1 kg [CI −1.8 to 1.5 kg]). In the second study, none of the 7 other muscle groups evaluated showed a positive change in strength.

Minor effects of hGH have been noted on basal metabolism with a slight decrease in respiratory exchange rate reflecting the preferential burning of fat rather than carbohydrate at rest. Additionally, there is very little effect on exercise capacity. The 6 studies evaluated used quite different protocols, and the results may be summarized as noting that lactate levels trended higher and that plasma free fatty acid concentrations and glycerol concentrations were significantly increased, reflecting the lipolytic metabolic effect of hGH, but the respiratory exchange ratio did not change.

These studies showed very little ergogenic effects of administered hGH in recreational athletes. They were of short duration and unlikely represent how elite athletes administer hGH, with reference to dose, duration, or other supplements, either legal or illegal. It is clear that many athletes abuse steroids in addition to the "noted" amounts of hGH. None of the studies would have been able to detect differences of 0.5–1.0% in "performance." These small differences are those that are relevant to the time (track events), distance, or height (field events) that separate the champion from any other finishing position.

Recently, hGH (19 $\mu g \cdot kg \cdot d^{-1}$) of 1 week's duration was noted to increase strength, peak power output, and IGF-1 levels in a group of abstinent dependent users of anabolic-androgenic steroids (211). Great care was taken to be certain that no anabolic steroids were detected in appropriately obtained urine samples. Body weight increased (likely water retention) as did peak power output. This is a very special group of athletes and is a single study, but it was quite carefully performed.

Adverse events were common in the larger group of studies and mirrored those of adult subjects administered hGH in what were at that time, child and adolescent doses. These included soft tissue edema, joint pain, carpel tunnel syndrome, and excessive sweating. Most are related to fluid retention and considered to be secondary to the GH effect on salt and water balance by the kidney.

Virtually all studies examining hGH supplementation had significant methodological limitations. These included limited examinations on strength and exercise capacity, short duration of supplementation, and doses not consistent with the method used by most athletes. Liu et al. (324) suggested that "Claims regarding the performance-enhancing properties of growth hormone are premature and are not supported by our review of the literature. The limited published data evaluating the effects of growth hormone on athletic performance suggest that although growth hormone increases lean body mass in the short term, it does not appear to improve strength and may worsen exercise capacity. In addition, growth hormone in the healthy young is frequently associated with adverse events."

Detection of GH Abuse

This has been quite a difficult task for the analytical chemists because the amino acid sequence of recombinant GH is identical to that of the main GH isoform secreted by the pituitary: unlike other peptide hormones, it has no *N*-linked glycosylation sites; its secretion is pulsatile with a short half-life (16–20 minutes); there are circulating GH-binding proteins; potential cross-reactivity with other peptide hormones (e.g., prolactin); and it is stimulated by exercise and stress. Blood sampling is required for all detection methods because less than 0.1% may be found in the urine. Its renal secretion is poorly understood and highly variable within and between subjects (250).

The analytical approaches rely on immunoassays as opposed to the more established doping tests for anabolic steroids, which depend on GC/MS technology. There are 2 general approaches to detection of doping with rhGH. The first approach (direct) measures the GH isoform composition by the differential immunoassay method (70). For this approach, one constructs pairs of antibodies whose primary focus is "all" of the isoforms of hGH and a second set that is virtually restricted to the 22-kDa isoform–the one that is 100% of the recombinant hGH. The first assay is called "permissive" (pituitary) and the second, specific (recombinant). The principle (rationale) is that the more one takes the rhGH (22 kDa), the less pituitary hGH (especially, 20 kDa) will be secreted, meaning that the ratio of the specific to the pituitary will rise. As an example, the ratio rises from 0.6 to 1.5 in subjects administered rhGH, but this assay would only

be valid within a few days of the last injection of rhGH. The validation of this technique requires knowledge (testing) of the effects of exercise on the recombinant to pituitary ratio, an independent confirmatory test (see below), knowledge of the "window of opportunity," and data from athletes, both recreational and elite. This method is unable to detect doping with pituitary-derived hGH or the abuse of the GH secretagogues, IGF-1 itself or in combination with its major circulating binding protein, IGFBP-3 (IGF-1/IGFBP-3) (250).

The second is the indirect approach in which specific analytes dependent on hGH (or IGF-1) would be measured. Variables from the IGF system and collagen/bone have been chosen because they change markedly during rhGH administration, and it appears that combinations of variables using discriminant functions are the most promising. Detection of rhGH supplementation is possible at least until 2 weeks after the last administration, although there is progressively decreasing sensitivity after the first week. Normative data in athletes have been established (233). The physiological changes in GH-dependent markers in adolescent athletes are far more dramatic than in older athletes, thus making it quite difficult to detect in this age range without constructing a complex algorithm that would depend more on maturational age than it would on the chronological age–another complication for doping control. Data using this approach have noted only minor effects due to trauma, micro-injury, or ethnic background (166). As with any assay, rigorous standardization is required and interference by concomitant drug abuse, especially anabolic steroids, is a likely complication. For the moment, the most informative combination of analytes is IGF-1 and procollagen III peptide levels and individual discriminant functions for men and women.

Direction of Future Research

Future research in the doping detection field will require the determination of combinations of GH-dependent analytes that are longer lasting than the ones currently used and perhaps other methods for the direct determination of the IGFs and GH secretagogues. It would seem that use of hGH (or other peptide hormones) manufactured by the major pharmaceutical companies around the world could be markedly diminished by adding, for example, an inert fluorescent marker that would be excreted in the urine. Detection of that (unnatural) marker might then be considered a doping offense. We suspect that that would markedly diminish but not stop doping offenses with these hormones.

The era of gene doping, for example, adding hGH or IGF-1 genes to specific muscles, is upon us. Experiments have been done in animals (37). No detection methods presently available could detect this type of doping.

Legal Issues

As is true for many legitimate drugs, physicians may prescribe off-label, meaning that trials for that particular condition have not been performed, but that it is "logical" to use a particular already approved drug for a specific patient. Recombinant hGH is quite different. It is *illegal* to prescribe hGH off-label for age-related conditions (anti-aging) or performance enhancement. Unlike most FDA-approved medications, hGH can only be prescribed for indications *specifically authorized* by the Secretary of Health and Human Services (for indications, see above). In addition, hGH is not considered a "dietary supplement" and is not subject to the DSHEA legislation because it is not administered orally and it had formerly been classified as a "drug" [FDCA 21 USC 321 (ff) (2) (A) (i)].

The precise language of the FDCA under section 303 [333] follows:

(f) (1) Except as provided in paragraph (2), whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 505 and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines authorized by title 18, or both.

(2) Whoever commits any offense set forth in paragraph (1) and such offense involves an individual under 18 years of age is punishable by not more than 10 years imprisonment, such fines as are authorized by title 18 or both.

(3) Any conviction for a violation of paragraphs (1) and (2) of this subsection shall be considered a felony violation of the Controlled Substances Act for the purposes of forfeiture under section 413 of such Act.

(4) As used in this subsection the term "human growth hormone" means somatrem, somatropin, or an analogue of either of them.

(5) The Drug Enforcement Administration (DEA) is authorized to investigate offenses punishable by this subsection.

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