Androgen Abuse by Athletes

Medical Grand Rounds

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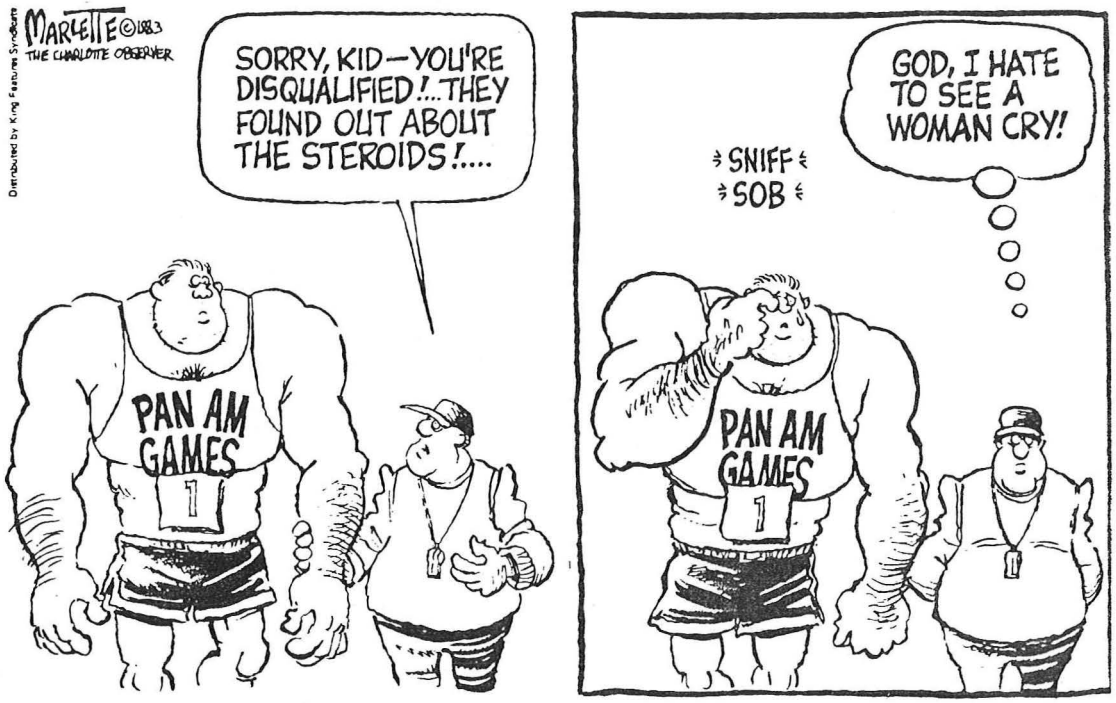

INTRODUCTION

Androgen abuse by athletes constitutes only a portion of the medical problem of androgen misuse by the general population (1) and only a minor aspect of the problem of the doping of athletes with drugs presumed to enhance athletic ability (2, 3). [Steroids account for about 15% of the drugs banned by the International Olympic Committee (4).] This particular form of drug abuse stems from the convergence of two separate conceptions (or misconceptions). The first was the recognition that the administration of androgens to hypogonadal males causes an increase in nitrogen retention and an increase in muscle mass and lean body weight (5). It followed that the differences in muscle mass between men and women are largely due to differences in testosterone levels, and it was assumed that a supraphysiological amount of androgen would do even more than the normal amount. It was also assumed that the anabolic (muscle promoting) and androgenic (virilizing) actions of the hormone are exerted by different mechanisms and that pure anabolic agents could be devised that would be devoid of or have minimal androgenic effects (6, 7). In fact, androgenic and anabolic effects are not due to different actions of the hormone but result from interaction of the hormone with the same receptor molecule in different tissues (1); furthermore, in men with normal levels of plasma androgens this receptor appears to be saturated. Thus, it has not been possible to separate the two types of actions at the pharmacological or physiological levels, and in normal men any anabolic actions obtained from exogenous androgens are inevitably limited in scope. The second impetus, at least in the United States, stemmed from international competitiveness in sports. According to a widely accepted account, John B. Ziegler, a physician for the U.S. weight lifting team was told by a Russian team physician at the 1954 world weight lifting championship in Vienna that some members of the Russian team used androgens (8). Ziegler returned home and began to experiment in American weight lifters with the various agents that had been developed as candidates for pure anabolic steroids (8), although he subsequently concluded that their effects were purely psychological (9).

Because of secrecy surrounding their use, a great deal of the information is based on hearsay and rumor, but there can be no doubt that athletes believed that the androgens enhance strength, and as a consequence, the "magic pills", obtained through legal and illegal sources, began to be used widely, despite the lack of clear evidence that they do in fact enhance athletic ability. The use spread through a variety of sports, professional and amateur, involving men and women, to the high school and junior high school levels and occurred despite the attempts of sports organizations to discourage their use (10) and despite a growing body of evidence that the toxic side effects of the agents outweighed any possible benefits to be derived. By the time of the 1964 Olympics, androgen use was widespread (11). The frequency of abuse varied from sport to sport, being most common in those influenced on weight and/or strength. For example, of athletes interviewed at the 1972 Olympics in Munich, 68% of those in middle or short distance running or in field events had taken steroids in preparation for the games, and in another survey all the weight lifters at the 1968 U.S. Olympic Training camp had taken steroids (12). The escalation of drug abuse resulted in the inclusion of the drugs on the list of banned substances for the 1976 Olympic Games in Montreal (13).

In some manner, fear that one's competitors will use them has a powerful coercive effect on athletes that overwhelms common sense and rational behavior

(14-16). Therefore, since their use appeared to be increasing, blood and urine assays of increasing sophistication were devised to detect androgen use, as a result of which nineteen competitors were disqualified at the Pan American games in 1983 and additional athletes withdrew rather than undergo testing (8). This issue has become widely publicized in the lay press and the weekly medical press, particularly with the recognition that prior use can sometimes be detected for six months or longer after cessation (8). By the time of the 1984 Olympics in Los Angeles and the Pan American Games in Indianapolis drug testing was being systematically applied (4), and it is now required by a variety of professional and amateur sports organizations, including post season college football games, despite some skepticism that testing does have an inhibitory effect on drug use by athletes (17, 18).

The purpose of this paper is to review the pharmacology of androgenic agents, to summarize what is known about the pattern of their abuse by athletes, to examine the question of whether androgens do in fact enhance athletic performance and, if so, how, to describe the side effects to be expected from their use, and finally to assess the state of the art drug testing.

ANDROGEN PHARMACOLOGY

Soon after the identification of testosterone as the principal androgen secreted by the testis it became apparent that the hormone itself cannot be given effectively either by mouth or by parenteral injection. Oral administration is followed by rapid absorption into portal blood and first pass degradation by the liver so that small amounts reach the systemic circulation. When testosterone is administered parenterally it is promptly absorbed from the injection vehicle and rapidly degraded so that effective levels are not sustained in the plasma. Therefore, it is necessary to modify the molecule so as to circumvent these problems. The aim of chemical modification is to retard the rate of absorption and/or catabolism so as to sustain effective blood levels for longer periods, to overwhelm the catabolic pathway with mass, or to enhance the potency of each molecule so as to achieve androgenic effects at lower blood levels of the drug (1, 19, 20).

Three general types of modifications of the molecule have proved useful (Fig. 1), namely esterification of the 17β-hydroxyl group (Type A), alkylation at the 17α-position (Type B), and modification of the ring structure of the steroid (Type C), particularly substitution at the 1,2,9, or 11 carbons. Most agents contain a combination of structural changes of the ring and either 17β-hydroxy esterification or 17α-alkylation (Fig. 2).

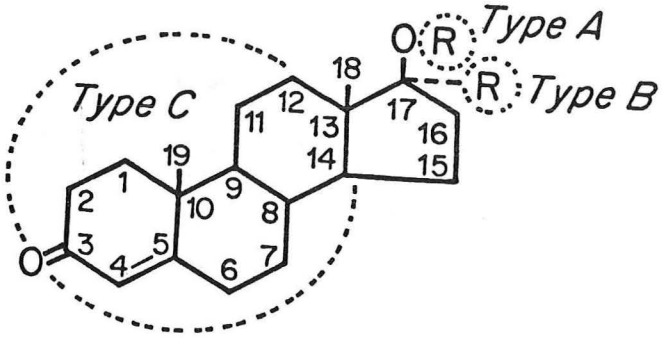

Figure 1: Categories of androgens commonly used pharmacologically. Type A, esterified androgens; Type B, 17-Alkylated androgens; Type C, Androgens with alterations of the steroid nucleus.

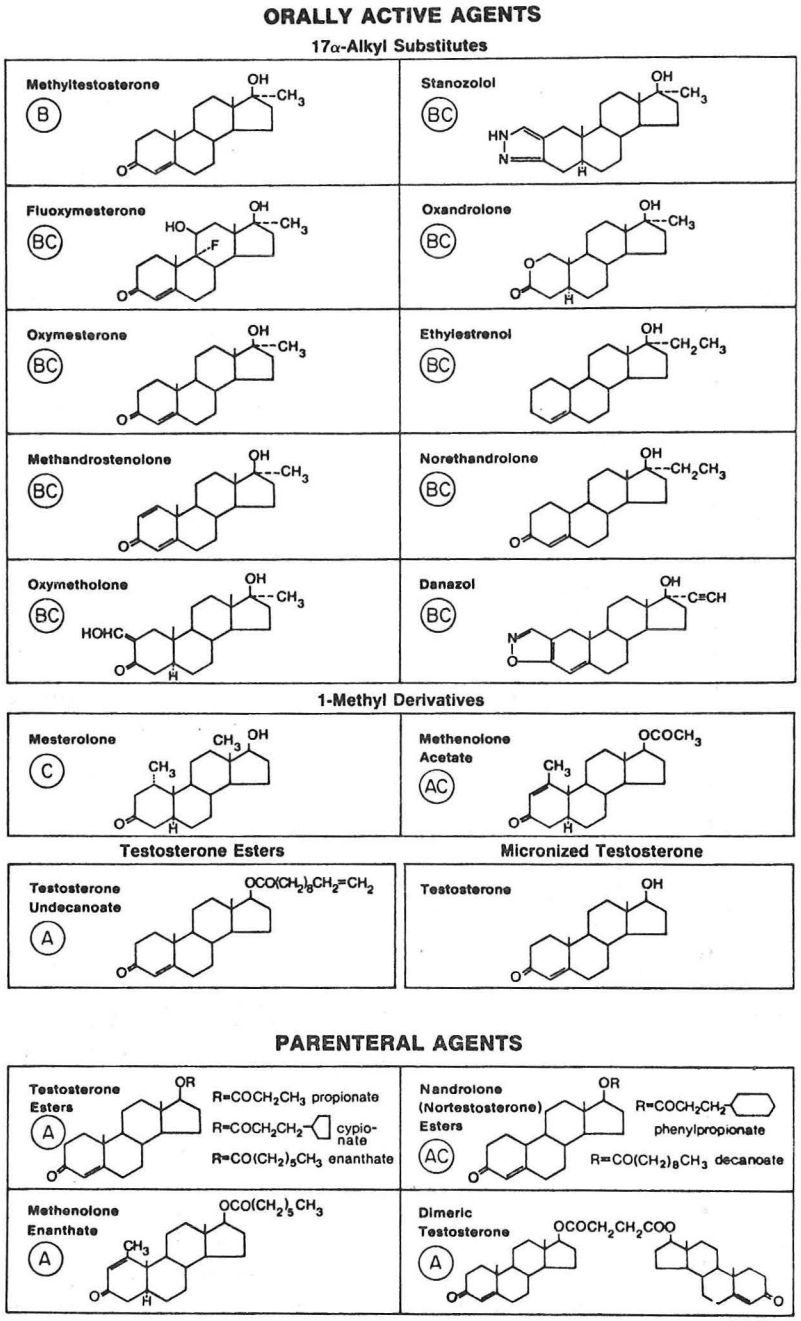

Figure 2: Some of the orally active and parenteral androgens approved for human use.

For oral administration four types of derivatives have been successful. Alkylation at the 17α-position with either a methyl or ethyl group is a common feature of most orally active androgens (21) (Fig. 2). Such derivatives are effective when given by mouth because they are slowly catabolized by the liver and hence pass through the liver to reach the systemic circulation in effective amounts. Oral administration can be accomplished by sublingual absorption from the buccal mucosa or by swallowing the drugs (22, 239). There is no known mechanism for the enzymatic removal of the alkyl groups in the body, and hence unique metabolites are present in blood and urine after their administration (4). Likewise, the 17α-alkylated steroids act within target cells as such. The usual clinical radioimmunoassays for testosterone cross react to a variable degree, and as a consequence, it is difficult to monitor blood levels and to monitor effectiveness of therapy (24).

Other alterations of the ring structure include alkylation at the 1 position of the steroid molecule (mesterolone and methenolone acetate) (25, 26); these substitutions, like the 17α-alkyl substitutions are not removed in the body and lead to unique metabolic degradation products (4). One 17β-hydroxy ester, testosterone undecanoate, has special features that make oral administration feasible. Testosterone undecanoate is so non polar that it is absorbed into the lymph rather than into the portal venous circulation, and as a consequence physiological blood levels of testosterone can be achieved at doses of approximately 120 mg/dy (27-29). Likewise, when testosterone in microparticulate form is ingested in large amounts (200-400 mg/dy) physiological blood levels can also be achieved (30). However, because of the rapid turnover of testosterone in plasma, testosterone undecanoate and micronized testosterone must be administered several times a day.

Parenteral administration of androgens is made possible by the esterification of the steroid with various carboxylic acids (19). This process decreases the polarity of the steroid, making it more soluble in the fat vehicles used for injection and hence slowing the release of the hormone into the circulation. In general, the longer the carbon chain in the ester the more fat soluble the steroid becomes and hence the slower the release into the circulation and the more prolonged the action. For example, testosterone propionate must be administered daily whereas testosterone cypionate and testosterone enanthate can be administered every one to three weeks (19). Even longer acting steroid esters are now undergoing trials (31). Although the esters themselves can be detected in plasma following parenteral administration, esterified androgen must be hydrolyzed before the hormone acts so that the effectiveness of therapy with testosterone esters can be monitored by routine radioimmunoassay of plasma testosterone following their administration (32, 33). These features, together with the fact that they are associated with minimal side effects, make the long acting esters the treatment of choice for male hypogonadism.

Alterations of the ring structure of the steroids have been utilized both for oral agents and for parenteral formulations (Fig. 2). Most such alterations have been adopted empirically. In some instances the effect is to slow the rate of inactivation; in others it enhances the potency of a given molecule or alters its metabolism. For example, 19-nor-androgens (norethandrolone, ethinyl estrenol, and nanadrolone) are more potent than testosterone because the absence of the 19 methyl group causes the more planar structure, like dihydrotestos-

terone, to fit more tightly into the binding site of the androgen receptor (34). The potency of fluoxymesterone and mesterolone may in part be due to the fact that they are not converted to estrogens in extraglandular tissues and hence, like dihydrotestosterone have "pure" androgenic actions (35). These various agents are virtually never converted in the body to testosterone itself and, hence, like the 17 alkyl derivatives circulate in plasma and are excreted into urine as unique metabolites. It is this aspect of their pharmacology that has made possible the detection of their use by athletes (4).

WHAT IS THE PATTERN OF ANDROGEN ABUSE BY ATHLETES?

Since the androgen receptor in normal men is saturated or near saturated with ligand, it follows that to be effective exogenous androgens must be administered in pharmacological amounts. Pharmacokinetic data have not been published in equal detail for all of the androgens available, but more importantly, one is dealing not with dosage based on rational criteria but with drug abuse. Our knowledge of the pattern of drug abuse is largely based on hearsay and rumor. Therefore, it is difficult to extrapolate from the established toxicological and pharmacological data to the situation in athletes. The only applicable data in most instances are derived from other pharmacological applications of the agents, such as their use in patients with bone marrow failure (36). The nature of this problem can be illustrated for methandrostenolone, one of the most widely abused oral androgen preparations. This agent was studied in some detail by Liddle and Burke who showed that maximal effects on nitrogen balance in adults are achieved by doses of 1.25-2.5 mg/dy, a dosage that usually produces no measurable effect on hepatic function (37). Doses in this range would thus be termed physiological and could be used for androgen replacement whereas higher doses would be pharmacological in nature. It is believed that when methandrostenolone abuse became widespread among athletes it was common to take what might be termed modest excess - 10 to 20 mg per day, and consequently most studies of the effects of the agents in athletic performance have been done in this general dose range (see below).

Whether these doses ever had any relation to the actual pattern of abuse is moot, because it is now apparent that in fact the agents are abused in what can be termed suprapharmacological amounts but in an intermittent fashion. For example, in one study 110 of 250 weight lifters interviewed in a single gymnasium in Chicago admitted to androgen abuse at some time (38); the athletes used the drugs in a cyclic manner, taking them for periods ranging from four to 18 weeks, alternating with drug holidays of one month to a year. Some of the athletes use a "pyramid" administration schedule, starting with a low daily dose and building to higher dosages. Other athletes use a "stacking" schedule in which several different preparations are taken simultaneously. These schedules usually involve a mixture of oral and parenteral agents. About half of the athletes "stack the pyramid" (38). And, in fact the so called stacked pyramid also appears to be a common practice of hormone abuse in Europe (39, 40) and among women athletes as well as men (41) (Fig. 3 and Table 1). In comparative terms, these doses range from 10 to 100 times the levels that have been utilized in most studies of the pathophysiology of the agents (37) and at least several times the ordinary pharmacological range. At the same time, intermittent use makes it difficult to extrapolate from studies in which the agents have been administered in ordinary pharmacological amounts but for long and continued periods. On the other hand, this pattern of abuse in which users observe

drug-free periods to "clean out the system" almost certainly minimizes the deleterious side effects, particularly those side effects that result after long term administration of the agents. The rationale of the cleanout period is clear. In the words of one such athlete the drug is stopped for four to seven weeks prior to competition so the "testing will be good", and "then I take 120 mg lasix during the 12 hours before the competition to wash out my system and make my urine dilute." (37).

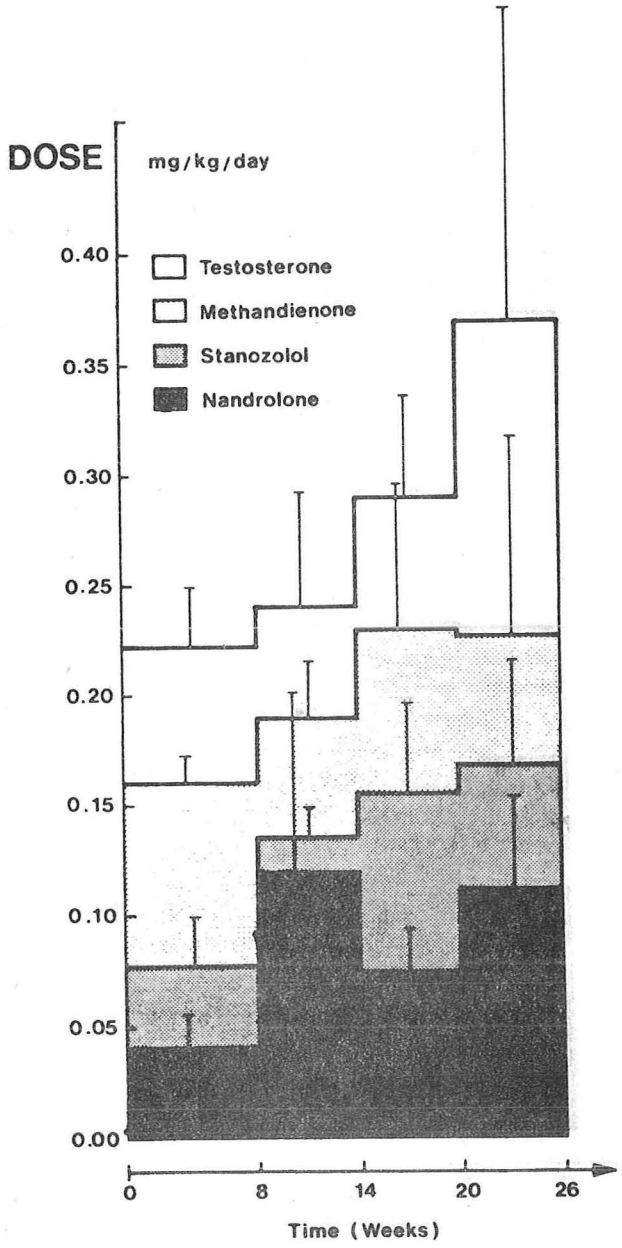

Figure 3: An example of a "Stacked Pyramid" of androgen self administration by one group of power athletes in Finland (From Ref. 40).

Table 1: Pattern of androgen use described by one female weight lifter (From Ref. 41).

Table 1.—Anabolic Steroids Reported by Heaviest User (Ten-Week Cycle)

Drug	Dose	Duration of Use, wk
Oral		
Stanozolol (Winstrol)	12 mg/day	10
Oxandrolone (Anavar)	10 mg/day	10
Mesterolone (Proviron)	50 mg/day	10
Injectable		
Stanozolol (Winstrol-V [veterinary])	50 mg/ 2 days	last 6
Methenolone acetate (Primobolan)	30 mg/ 2 days	last 4

Another aspect of the pattern of abuse deserves comment. Namely, some of the most common of the drugs abused are in fact not human but veterinary drugs (41) (Fig. 4). Others are marketed for human use in other countries but not approved by the FDA for use in the U.S. (43); the latter are either purchased by athletes outside the U.S. or smuggled across the border by drug pushers (44). This feature obviously complicates the monitoring of patients for side effects because careful human toxicity data have not been published for most of these agents; it is frequently the case, however, that such drugs are not approved for use in this country or for human use by any country due to their toxicity. Because of widespread abuse of methandrostenolol (and the fact that it has no medical usefulness), its manufacture has been stopped in this country and, more recently, world wide. As a consequence, it has been displaced in most areas as the most commonly abused androgen, but it still continues to reach the market in pirated form. The safety (and sterility) of these counterfeit and bogus drugs, some made in underground laboratories, has not been established, and many are believed to contain unknown or unexpected ingredients (45).

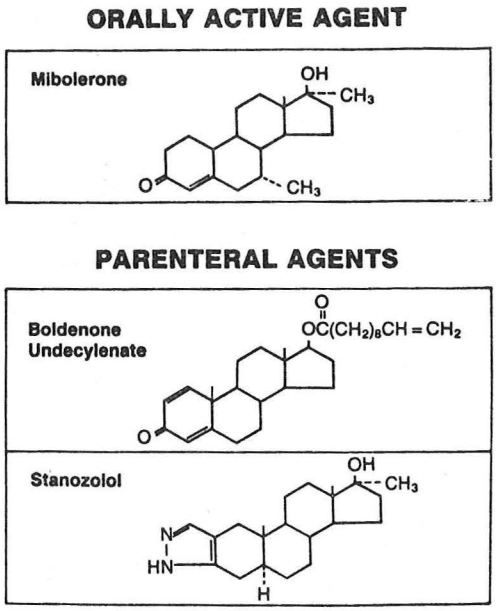

Figure 4: Veterinary androgens that are frequently abused by athletes.

The fact that veterinary drugs are abused by humans raises the question of how androgenic agents are obtained by athletes. Here again, one is dealing largely with hearsay. In one study of the pattern of abuse about a fifth of steroid users obtain them by prescription from physicians (17), a mixture of deluded sports physicians who believe that they are doing the right thing and physicians who are on the borderline of ethical practice. In Scandinavia, prescriptions to enhance athletic performance of any drug is illegal, and the suggestion has been made that androgens should be classified as controlled substances by the FDA (46). The remaining four fifths of these androgens, including veterinary drugs, are obtained on the black market (44, 45), which is largely operated by trainers and others on the periphery of the world of sports.

As is the case for other drug undergrounds, the profits made by the pushers of these drugs are enormous (44, 45), and the federal drug enforcement authorities have broken up and prosecuted several nationwide networks of traffic in the drugs (45).

DO ANDROGENS ENHANCE ATHLETIC PERFORMANCE?

After thirty years of use it is still not clear whether androgens do in fact enhance athletic performance. The reasons for this uncertainty are several. First, it is necessary that their use be blinded. After all, androgens are taken for this purpose by athletes who are participating in training programs; both the physical attributes of athletes and their motivations vary, and both of these factors influence the effectiveness of training. The nature of this dilemma is established by an important study done by Ariel and Saville (47). Fifteen varsity athletes were studied after two years of hard weight training. For four months prior to the actual experiment all subjects trained for 5 days each week and were tested under standardized conditions; they were informed during this preliminary period that the most improved lifters would be given methandrostenolone. Six of the subjects were so chosen, given access to research papers suggesting strength gain associated with androgen use, and then given by the University Health Service a daily placebo, which they were told contained 10 mg of methandrostenolone, while they continued the training program (Figure 5). By three of four criteria the improvement during the placebo period was significantly greater than during the previous training. Taking the placebo apparently supplied the necessary psychological benefits to make possible strength gains above that to be expected from a reasonable temporal progression. This study is well designed, particularly in regard to the prior training, and it can only be concluded that extreme caution must be exercised in assessing the effects of any specific treatment on performance.

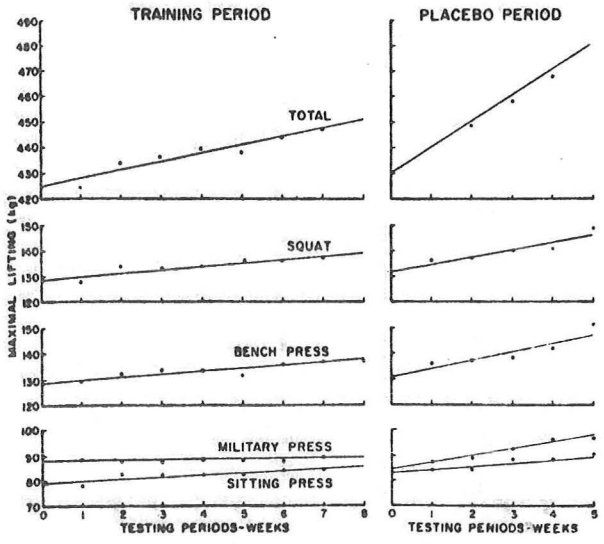

Figure 5: Effect of placebo administration on maximal lifting by 6 trained weight lifters (From Ref. 47).

In fact, most published studies in this area are not blinded, and the nature of the problem is illustrated in a well publicized study by Johnson and O'Shea (48). They compared the effects of 10 mg methandrostenolone daily in twelve eager weight lifters who were willing to take the drug with the performance of twelve athletes who were unwilling to take the agents because of fear about its side effects. Over a three week period the gains in strength in the treatment group were a few percent greater by several criteria. One can only conclude that this study is invalid since neither motivation nor innate capacity could be controlled. Similar or worse problems, including self administration and varying doses of different steroids, make it impossible to interpret many studies published in this area, some that report no effects (49, 50) and some that report positive effects of androgens on strength (51-57). In other instances, blinding was attempted but because of side effects produced by the drugs, the code was broken by the participants so that the study was compromised (58). Indeed, this problem may be pervasive because minor side effects (acne and shrinkage of the testes) may make recipients aware that they are receiving drug rather than placebo. Still other published studies are not reported in sufficient detail to make assessment practical (59).

A second problem is that the various published experiments utilize different androgens, different dosage schedules, different training programs, different assessment criteria, different diets during the study period, variable degrees of training prior to the study period, different numbers of subjects, and different statistical treatments of data. Certain of these variables make it difficult to interpret some of the negative studies as well as some positive studies (60).

Third, effects of variables on athletic performance become progressively more difficult to assess the better the calibre of the athlete. For example, a 1% difference in speed, which would be difficult to document between groups, might make a profound difference in the performance of an individual athlete at the level of international competition, where a fraction of a second may be significant.

Despite these various problems in design and execution, sixteen studies that examine the effect of androgens on muscular strength appear to be adequately blinded and designed (12, 61-75) (Table 2). The data in Table 2 have been separated into two groups - nine studies that observed no difference in muscular strength (12, 61-68) and seven studies in which significant enhancement of muscular strength was reported (69-75). Of the seven positive studies two (71, 74) are reported in such a way as to make uncertain the validity of the interpretation; e.g., differences in mean values are slight, and the ranges of variation are not provided so that it is not clear whether the statistics are in fact valid. The other 5 studies appear to be valid. Four of nine negative studies in terms of strength and four of the 7 positive studies were associated with similar degrees of androgen-mediated weight gain (1.5-2 kg). The nature of the weight gain in terms of body composition is uncertain and probably consists of combinations of water retention, increased blood volume, and increases in lean body mass (see below). The most interesting pair of negative and positive studies (67, 75) were performed by the authors and utilized similar design - namely double blind crossover with a gigantic dose of methandrostenolone (100 mg/dy), and both were associated with a weight gain and increased muscle mass. The only difference between the studies was that the subjects in the negative

TABLE 2 EFFECTS OF ANDROGENS ON WEIGHT, MUSCLE MASS, AND STRENGTH IN ATHLETES

NEGATIVE STUDIES

REF. #	61	62	63	64	65	12	66	67	68
DRUGS	Methandro-stenolone 20 mg/dy	Stanozolol 6	Nandrolone Decanoate mg/kg of 3 weeks	Mesterolone 75-150 mg/dy	Stanozolol 6 mg/dy	Methandro-steneolone 10 mg/dy	Methandro-steneolone 20 mg/dy	Methandro-steneolone, 100 mg/dy	Testosterone Cypionate, 100 mg/wk; Nandrolone Decanoate, 100 mg/wk
WEIGHT CHANGE	No	Yes (1.7 Kg)	No	No	No	Yes (4.4 Kg)	No	Yes (3.3 Kg)	Yes (1-5.2 Kg)
CHANGE IN MUSCLE MASS	No	Not Measured	No	Slight ↑ in Thigh Mass	No	Not Described	No	Yes	Yes No
NUMBER OF SUBJECTS/GROUP	7-8	6-7	13-15	10-11	7	6	10	11	10
PERFORMANCE CRITERIA	Isometric Muscle Strength	Isometric Muscle Strength	Bench Press & Torque Maximum	Isometric Muscle Strength	Running Speed & Arm & Leg Strength	Dynamic and Static Strength	Isometric Muscle Strength	Weight Lifting	Peak Torque Output
DURATION OF STUDY (WEEKS)	16	7	9	8	3	6	12	6	3
TRAINING PRIOR TO STUDY	Yes (Two groups)	No	Yes	Yes	Yes	Yes	Yes	No	Yes
PROTEIN SUPPLEMENT TO DIET	Yes (Two groups)	No	No	Yes	Yes	Yes	Yes	No	Yes

POSITIVE STUDIES

REF. #	69	70	71	72	73	74	75
DRUGS	Methandro-stenolone 10 mg/dy	Methandro-stenolone 10 mg/dy	Methandro-steneolone 10 mg/dy	Methandro-steneolone 15 mg/dy	Methandro-steneolone 15 mg/dy	Methandro-steneolone 5 mg/dy	Methandro-steneolone 100 mg/dy
WEIGHT CHANGE	Yes (2.2 Kg)	Yes (1.7 Kg)	Yes (2.41 Kg)	Not described	Not described	Yes (1.3 Kg)	Yes (3.6 Kg)
CHANGE IN MUSCLE MASS	Not Measured	No	Yes (5 of 8 tests)	Not described	Not described	Not described	Yes
NUMBER OF SUBJECTS/GROUP	9	8	12	3	5	15	7
PERFORMANCE CRITERIA	Dynamic Strength	Bench Press; Squat	Dynamic and Static Strength	Dynamic and Static Strength	Dynamic and Static Measurement	Pull up, Sit down, Broad jump	Leg & Arm Strength
DURATION OF STUDY (WEEKS)	4	5	7	5	4	13	6
TRAINING PRIOR TO STUDY	Yes	Yes	Yes	Yes	Yes	No	Yes
PROTEIN SUPPLEMENT TO DIET	Yes	Not Mentioned	Yes	Not Mentioned	Not Mentioned	Not Mentioned	Not Mentioned

study (67) were not trained weight lifters prior to the start of the experiment whereas the positive study (75) involved previously trained weight lifters. However, 7 negative studies (12, 61, 63-66, 68) also involved previously trained weight lifters. It is also unlikely that protein supplementation to the diet has any effect on strength since several of the negative studies included such supplementation (61, 64-66, 68).

In summary, neither enhancement of weight nor improvement in strength can be demonstrated consistently when androgens are administered double blind to athletes. Most reviewers in the field (1, 61, 76-78) have consequently concluded that at a scientific level a positive relationship between androgen use and athletic performance is unproven and that effects on weight and muscle mass are inconsistent. Admittedly, the total number of athletes studied carefully is small, and it is possible that androgens work in some individuals but not others and that if the individual groups had been larger either positive results might have disappeared or negative results might have become positive. Even if one accepts the positive results as valid, however, the beneficial effects are limited to effects on strength and weight, are inconsistent, and when present are not very impressive.

The inconsistency in the supporting evidence has had no effect whatsoever on androgen abuse for a variety of reasons. One, the published studies do not involve administration of the drugs in a fashion comparable to "stacking the pyramid". Second, there is a widespread belief among coaches and sports physicians that the breaking of athletic records in the recent past correlates with androgen use. For example, the mean weight of the ten best weight lifters at the annual Norwegian championships increased by 18 kg between 1962 and 1982, and this phenomenon has been attributed to androgen abuse (79) (Fig. 6). Indeed, Payne has attributed the consistent breaking of world records in a variety of sports since 1950 to androgen abuse rather than improved training techniques and/or nutrition (80). Moreover, Forbes analyzed the relation between lean body mass and androgen use and has suggested that the relation between lean body mass and androgen use is with the total dose; namely after administration of about 20 grams of exogenous androgen, lean body mass increases about 18 kg, an amount of weight gain similar to the sex differences in lean body mass generated by endogenous androgens in boys during the pubertal years (80) (Fig. 7). While the studies on which his conclusions are based are not controlled, they do provide support for the objection that no blinded study has been done of the "stacked pyramid". Third, athletes themselves and their trainers continue to believe the uncontrolled studies and to attribute any positive results to steroids rather than to the training program or innate ability. Because of this pervasive belief in a beneficial effect, the American College of Sports Medicine has changed its official position (not on the basis of new evidence) from one that maintained that they are ineffective and dangerous (10) to one that now concludes that they are effective in some athletes but dangerous (82).

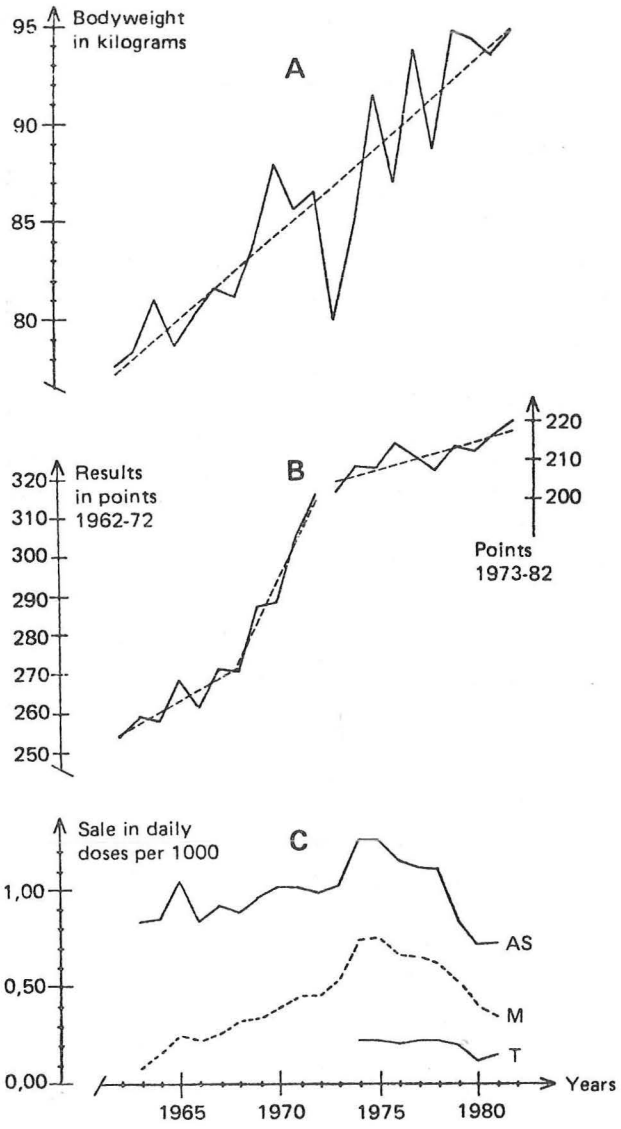

Figure 6: Comparison of body weight and strength of the ten best weight lifters in Norway with androgen sales 1962-1982 (From Ref. 79).

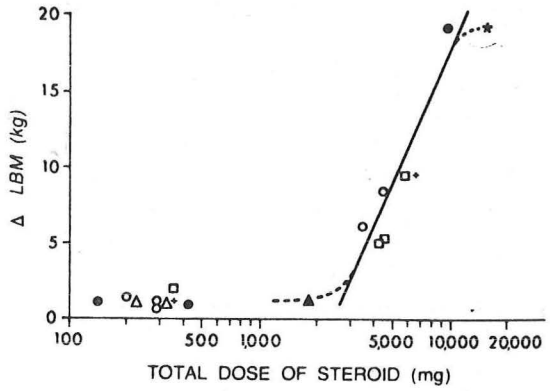

Figure 7: Semi-logarithmic plot of increment in lean body mass against total dose of androgen (From Ref. 81).

IF ANDROGENS ENHANCE STRENGTH, HOW DO THEY WORK?

Androgens like other steroid hormones are believed to exert their fundamental physiological actions via interaction with a specific intracellular receptor protein in target tissues; the hormone-receptor complexes in turn interact with receptor sites within the chromosomes to promote the transcription of genes and hence the synthesis of messenger RNA molecules. The general schema by which androgens work is summarized in Figure 8. Muscle is one of the target tissues for androgen. While all skeletal muscles probably respond slightly to

androgens, there is considerable variation among species as to the sensitivity of individual muscles and muscle groups to the hormone. Muscles in which there is a profound response to androgen include the temporalis muscle of the guinea pig (83), the levator ani muscle of the rat (84, 85), the forearm muscles of the frog (86), and in man the muscles of the pectoral and shoulder region (87). For example, castration of the frog causes a profound decrease in the cross sectional area of the flexor carpi radialis and flexor carpi centralis muscles of the forearm but only a trivial effect on the leg muscles (86). Similarly, testosterone causes a profound increase in the fast-twitch isoform of the myosin heavy chain in the temporalis muscle of the guinea pig but not in other guinea pig muscles (83). However, the levator ani/bublbocavernosis muscle group in the rat is the best studied of the androgen-dependent muscles. The correlation of the androgen receptor is many fold higher in these muscles than in the other rat muscles (88). Furthermore, the androgen receptor protein in this muscle group is a typical androgen receptor that binds dihydrotestosterone about 10 times as avidly as testosterone (88), and dihydrotestosterone is about 2½ times as potent as testosterone in causing growth of these muscles (89). However, there is little if any 5α-reductase in skeletal muscle (90), and consequently dihydrotestosterone in muscle is probably derived from circulating dihydrotestosterone. In male rats, dihydrotestosterone accounts for half or more of androgen in the nuclei of the levator ani muscles (91), and following the administration of testosterone to castrated rats dihydrotestosterone also counts for about half of the intranuclear androgen (92). [In human skeletal muscle contact, testosterone is the predominant androgen recovered in biopsy samples from both men and women (93, 94)].

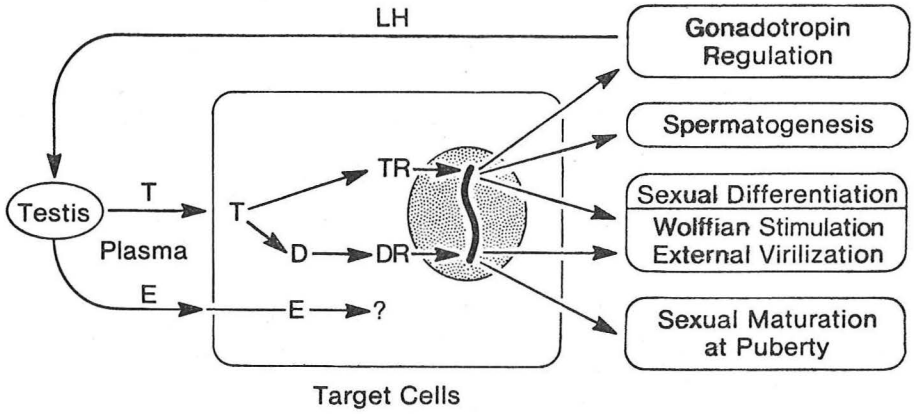

Figure 8: Schematic representation of the mechanism of action of androgen. T, testosterone; D, dihydrotestosterone; R, receptor protein; LH, luteinizing hormone.

In view of the fact that dihydrotestosterone binds more avidly to the receptor protein and is more potent in bioassay studies it was my assumption for a time that dihydrotestosterone is the effective androgen of muscle, but in fact inhibitors of 5α-reductase in the castrate rat given testosterone do not blunt the myogenic effects of testosterone (95). It thus appears that testosterone is equally as myogenic as dihydrotestosterone and that either hormone can mediate a

maximal myotrophic effect. Most critically for this purpose, supraphysiological doses of androgen do not produce additional muscle growth beyond that expected from the normal levels of male hormone (92) (Fig. 9). The reason for this limitation in androgen-mediated growth is believed to be mediated at the level of the androgen receptor itself. The total content androgen receptor does not change following denervation or disuse of muscle (96, 97), a finding that is in keeping with the view that denervation does not influence the response of frog muscle to androgen administration (86). However, the level of muscle androgen receptor, like that in other androgen dependent tissues (98), is under exquisite control by gonadal steroids themselves in that estrogen enhances and androgen down regulates the level of receptor in the levator ani muscle (99) (Fig. 10). In brief, the response of muscle to androgen involves a typical androgen-receptor system, and the graded response of different muscle groups to androgen administration can be explained by variations in the level of androgen receptor within the muscles. However, as is characteristic of other androgen response systems, the capacity of muscle to respond is limited at the point the androgen receptors become saturated, e.g., at normal levels of testosterone for the adult male. If pharmacological doses of androgens promote additional muscle growth in normal men they probably act by another mechanism.

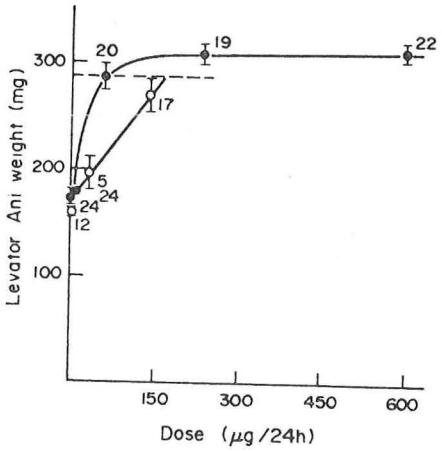

Figure 9: Weight of the rat levator ani muscle after treatment with testosterone (o) or dihydrotestosterone (o) (From Ref. 92).

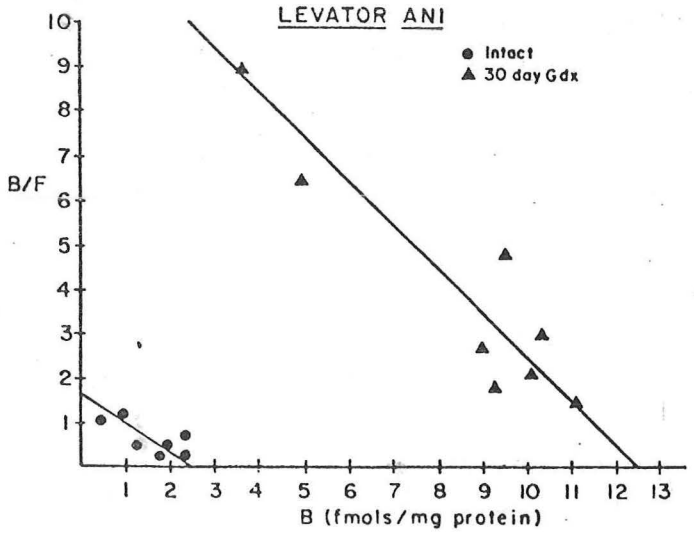

Figure 10: Effect of castration on the amount of androgen receptor in the levator ani muscle of the rat (From Ref. 99).

At a theoretical level, androgens might promote positive nitrogen balance by any of several mechanisms not involving the androgen receptor, for example by serving as antagonists to the catabolic effects of glucocorticoids. Indeed, several androgens are effective inhibitors of the binding of dexamethasone and cortisol to the glucocorticoid receptor that is known to be present in skeletal muscle and that is believed to mediate the catabolic actions of the hormone (100). The level of the glucocorticoid receptor in levator ani muscle increases following castration (101), and glucocorticoid antagonists can retard in part

the atrophy of the levator ani muscle following castration (102, 103). Thus, the thesis has been proposed that androgens in pharmacological amounts act as glucocorticoid antagonists and hence promote positive nitrogen balance independent of the androgen receptor. [A similar mechanism but involving the estrogen receptor has been proposed for the antagonistic effect of androgen on estrogen-mediated breast growth (104)]. If this hypothesis is correct, then at least two predictions could be made as to the consequences of an antiglucocorticoid effect in subjects with intact pituitary and adrenal gland. One, in the steady state ACTH levels should rise and hence glucocorticoid secretion should increase following the administration of androgens in pharmacological amounts; this is in fact the case in that excretion of free cortisol in urine approximately doubles following ingestion of 100 mg/dy methandrostenolone (75) whereas levels of cortisol binding globulin are unchanged (105). Two, in normal men, any positive effect of androgen on nitrogen balance in the steady state should be transient and should be reversed when glucocorticoid secretion rises to overcome the block in glucocorticoid action; this again is what happens. When androgens are administered to men with intact testes, positive nitrogen balance is slight and only lasts a few days (106). Thus, the available data appear to be compatible with the possibility that androgens may enhance lean body mass by acting as antagonists to glucocorticoids. The mild hyperadrenal state that results is of no moment as long as levels of the antagonist are high and rapidly reverts to normal when androgens are discontinued.

The increase in body weight after androgen abuse could be due to still other mechanisms. The increases in body potassium and nitrogen after massive doses of methandrostenolone are too large in proportion to the weight gain for this to be attributed solely to gain of normal muscle (67, 75). A part of the weight gain may be accounted for by effects on blood volume itself. Androgen in pharmacological doses causes an increase in hematocrit of about 1 g/dl in most men (107-109), and, more importantly, total blood volume may increase by 15% or more (110). In fact, weight changes appear to be best explained by an increase in blood volume (110), and in those men who do experience an increase in blood volume the effect on competitive performance might be similar to that achieved by the practice of blood doping in some sports (111). This effect on blood volume is presumably mediated by the enhancement by androgen of erythropoietin synthesis (112). In part, the increased body weight could also be due to sodium retention which under some circumstances can be appreciable (113); the mechanism for this phenomenon is uncertain.

In summary, the increase in weight produced by pharmacological doses of androgens in men may in part be mediated by enhancement of lean body mass (involving the androgen receptor itself or via antiglucocorticoid actions of the agents), in part by an increase in blood volume, and possibly by undefined mechanisms as well. Whether the lack of consistency of the increase in weight is due to some undefined variation in dosage or in specific pharmacological actions of the different drugs or is due to variability in response among men is also unclear.

HOW DANGEROUS ARE ANDROGENS?

Analysis of the side effects of androgens is complicated by problems of definition (114). Indeed, some physiological actions of the hormone (via the androgen receptor) can be defined as toxic effects when they occur in an inappropriate setting; e.g., virilizing actions in young boys and in women. Other side effects are the consequence of metabolites of the drugs, and since different androgens are metabolized differently the side effects vary as well. For example, some but not all androgens can be metabolized to estrogens and hence cause both feminizing and virilizing effects. Still other side effects result from actions of the drugs that have no relation to hormonal effects, as in the case of the impairment of hepatic function by the 17-alkyl androgens. Finally, the mechanisms - whether hormonal or toxic - by which some side effects occur are unclear; this is the case, for example, in regard to the effects of androgens on lipoprotein metabolism.

There is also wide variability among subjects as to the incidence of the various side effects, just as there is variability among normal men in the degree of virilization at puberty. In part this is age related; children are particularly susceptible to the virilizing, feminizing, and toxic effects of the agents. In addition, coexisting clinical conditions may influence the appearance of side effects; feminizing side effects are more common when hepatic function is impaired. Furthermore, the relation between duration of treatment, pattern of administration and dosage, and drug-drug interactions for the various agents have never been explored systematically. This issue is of even more concern in regard to the problem of drug toxicity in athletes because most reports that conclude that the side effects are innocuous are based on informal surveys of drug abusers rather than systematic examinations of hepatic and renal function in such people.

Virilizing Side Effects The virilizing effects of androgens in adolescents and in women are outside the central focus of this review (114). Indeed, these agents have a profound capacity to promote premature epiphyseal closure and induce premature virilizing actions in children of both sexes (115). The virilizing side effects in women, including hirsutism, acne, coarsening of the voice, hypertrophy of the clitoris, and male pattern baldness, are largely irreversible when the agents are discontinued (116-119). The nature of these actions precludes systematic investigation of the effects of the agents in women and children but has not prevented their abuse by these groups (41, 115). As a consequence, even less is known about the side effects of the agents in women and children than in men.

The administration of testosterone esters to normal men in amounts sufficient to replace the normal daily testicular secretion (equivalent to 5-10 ng/dy) has little physiological effect (120). When the plasma testosterone is raised above the physiological range, the plasma levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) are decreased via the classical feedback action of androgens on the hypothalamic-pituitary axis. As a consequence, testicular volume is decreased about 20%, and sperm production is uniformly decreased by 90% or more. The ejaculate volume remains unchanged (109, 121-124). The administration of androgens other than testosterone in comparable amounts results in a decrease in plasma testosterone but otherwise identical changes in plasma gonadotropin levels and sperm counts (125, 126).

These properties of androgens were the basis for their trials as male contraceptives, the hope being that sperm production could be inhibited under circumstances in which androgen action is maintained. Such therapy is associated, at best, with only slight enhancement of the constellation of androgen effects mediated by the androgen receptor; for example, sebum production increases only slightly under circumstances in which testicular volume decreases by 30% (127). However, when plasma testosterone is raised above the physiological range, body weight increases about 3% (partly due to volume expansion), hemoglobin rises about 1 g/dL, and serum estradiol doubles (109). Although in trials of androgens as male contraceptives, inhibition of spermatogenesis is rarely complete (109) the "stacking" protocol for hormone administration has a more profound inhibitory effect on gonadal function (40, 56, 57) and in fact results in an almost universal azoospermia (128) (Table 3). Interestingly, following such periods of drug abuse, a relative hypogonadism can persist for long periods after the drugs are discontinued (129) a state that may in part be due to a relative hypogonadotropic state and in part due to testicular refractoriness to gonadotropin (130). The extent to which this long term effect is due to persistence of these agents within the body tissues [(a particular problem with nanadrolone decanoate (131)] as compared to actions that outlast the hormones themselves is unclear, and it is also unclear whether the testicular damage can in part be explained by elevation in plasma estradiol in some instances (56, 109). The critical point is that hypogonadism, including azoospermia, can persist for 12 weeks or longer after discontinuation of the drugs (40, 56, 132).

Table 3 Effect of a six months stacking regimen of androgens (averaging 50 ± 24 mg/dy) in sperm production in 7 power athletes (From Ref. 128).

Variable	Time (months)											
	1		3		6		9		10 1/2		13	
	SC	TNo	SC	TNo	SC	TNo	SC	TNo	SC	TNo	SC	TNo
Use of drugs in study group	–	–	+	+	+	+	–	–	–	–		
Case 1					0	0					0	0
Case 2	2	7	0	0	0	0	6	20				
Case 3	1	4	0	0	0	0	0	0	0	0	85	286
Case 4	1	2	0	0	0	0	5	13	75	287		
Case 5	16	56	0	0	0	0	17	65	53	217		
Case 6	82	295	2	5								
Case 7	21	63	0	0	0	0						
Mean ± SD	20.5 ± 31.3	71.2 ± 113.0	0.3 ± 0.8	0.8 ± 2.0	0 ± 0	0 ± 0	7.0 ± 7.2	24.5 ± 28.2	42.7 ± 38.6	202 ± 21.2		
Case 8	14	42	237	474	49	59						
Case 9	63	234	44	136	34	110						
Case 10	34	110	14	62	48	200	41	196				
Case 11	205	574	54	194	77	229	102	406				
Case 12	135	188	199	238	138	220	180	413	131	235		
Case 13	54	204	137	357	94	328	78	288	81	307		
Case 14	24	55	74	155								
Mean ± SD	75.6 ± 69.6	201.0 ± 180.4	108.4 ± 84.4	230.9 ± 141.2	73.3 ± 38.5	191.0 ± 95.0	100.3 ± 58.8	326.8 ± 103.8	106.0 ± 36.4	271.0 ± 50.9		
	$P<0.05$	NS	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$				

Empty space indicates that no semen sample was delivered

Feminizing Side Effects In both men and women testosterone and androstenedione are converted in extraglandular tissue to the estrogens estradiol and estrone (133). Although the conversion of each androgen analogue to estrogen has not been demonstrated it is assumed that most steroids with a delta 4,3 keto configuration can be converted to estrogens and that feminization is mediated by the estrogenic metabolites of the parent steroids. The structures of certain androgens including fluoxymesterone, mesterolone, and (probably) stanazolol preclude their aromatization to estrogens, and it is likely that feminizing side effects are more common following administration of testosterone esters than after other androgens due to the fact that testosterone is such a good substrate for the aromatase enzyme. For example, testosterone is a better substrate for estrogen biosynthesis than is 19-nortestosterone (134). Indeed, in men on stacking regimens plasma estradiol levels can rise seven fold to levels comparable to those normally seen in ovulating women (40). The most common feminizing sign in men is development of gynecomastia, and indeed gynecomastia is common in weight lifters after such stacking regimens (40, 56). Gynecomastia is particularly pronounced in children given androgens, possibly due to a greater capacity for extraglandular aromatization, and in subjects with underlying liver disease, probably due to a diminished rate of hepatic clearance of the parent steroids and/or diminished clearance of the estrogenic metabolites (135).

Toxic Side Effects All 17α-alkylated androgens studied so far consistently produce bromsulphalein retention and commonly cause other liver function abnormalities such as increase in plasma alkaline phosphate and conjugated bilirubin (136-139). When bromsulphalein retention exceeds 40% jaundice almost invariably results. Occasionally, jaundice can be due to a hypersensitivity reaction (140). Other changes in liver function induced by 17α-alkylated drugs include increase in several plasma proteins (141) and a decrease in the conjugation of adrenal steroids by the liver (142). The abnormalities of liver function ordinarily subside when the drugs are stopped (143).

More serious hepatic complications include development of peliosis hepatitis (blood filled cysts in the liver) or hepatoma. These disorders were originally described in subjects with aplastic anemia, many of whom have Fanconi's anemia, itself a predisposing factor for malignancy (1). However, these tumors have been described in patients receiving androgens for other reasons including male hypogonadism (144, 145) and in one athlete who abused androgens for several years (146). Significant hepatic lesions are common in patients on long term treatment with 17-alkyl androgens (147) and have been described in one patient review a 10 alkyl derivative (149) but are believed not to occur in subjects receiving testosterone esters. In some individuals such tumors may regress and follow a benign course after discontinuation of the drugs; in others the course is rapidly fatal. Whether the rare occurrence in an adult of Wilms tumors (150) or the early development of a prostatic carcinoma (151) is causally linked to longstanding methandrostenolone abuse or was coincidental to its use is unclear.

Side Effects of Unknown Mechanism Some side effects of androgen use occur by uncertain mechanisms. Sleep apnea occurs in occasional men given large amounts of testosterone esters (136), possibly a consequence of an increased hematocrit (153). Some degree of sodium retention is a common consequence of therapy with all androgens, but the amount of retained sodium is usually minor except in patients with underlying renal failure (154). Occasional hyperlipidemia has

also been reported, the provenance being unclear (155). Likewise decreased glucose tolerance and insulin resistance have been observed in power lifters on a stacking regimen of androgens long term (156).

A more common finding is a depression in high density lipoprotein and elevation in low density lipoprotein with a resulting alteration in the ratio of the two lipoproteins in plasma that is believed to be associated with accelerated atherosclerosis (157-166) (Table 4). Indeed, the alterations in serum lipoprotein profiles are so consistent in androgen abusers and particularly following the stacking regimen that one would expect to see a significant increase in atherosclerotic events in such athletes. The fact that such an increase has never been documented suggests either that a lag phase is required for such a phenomenon to become manifest or that intermittent use followed by so called washout periods mitigates the long term consequences of their abuse. It is of interest that depression of HDL-C is less striking after the administration of testosterone esters (164, 166) (Table 5) than after the stacking regimens, suggesting that the greater decrease in those studies is either a toxic manifestation of hepatic damage or is dose related in some other manner.

Table 4 Studies of the Effects of Androgens on HDL-Cholesterol Levels in Athletes

Study	157	158	159	160	161	162	163	164*	165
Year	1983	1984	1984	1984	1984	1985	1985	1986	1986
Number of Subjects	4F, 2M	9M	14M	14M	12M	5M	50M	8M, 1F	3F, 9M
Agent	Stanazolol	Oxymethalone; Methandros-tenolone; Testosterone esters	Methandros-tenolone; Testosterone cypionate; Nandrolone decanoate	Nandrolone methandros-tenolone; Stanazalol; Testosterone esters	Various drugs	Methandros-tenolone; Testosterone cypionate	Various drugs	Testosterone cypionate; Nandrolone decanoate	Multiple drugs
Admini-stration	6 mg/dy	Stacking regimen	Stacking regimen	Stacking regimen	Stacking regimen	Stacking regimen	Stacking regimen	100 mg/week x 3	Stacking regimen
Findings	HDL-C ↓, LDL-C ↑	Profound ↓ in HDL-C	Profound ↓ in HDL-C, ↑ LDL-C	↓ HDL-C	↓ HDL-C, ↑ LDL-C	↓ HDL-C ↑ LDL-C	↓HDL-C	↓ HDL-C	↓ HDL-C

* only blinded study and the least impressive effects

Table 5: Effect of testosterone cypionate and nandrolone deconoate on high density lipoprotein levels in athletes (From Ref. 164).

Measure	Baseline			Placebo			Testosterone			Nandrolone decanoate			Probability of treatment effect	Source
	*G mean	s.e.m.	†F	G mean	s.e.m.	F	G mean	s.e.m.	F	G mean	s.e.m	F		
HDL-C (mg/dl)	49.1	1.1	54.0	46.5	1.1	54.0	42.6	1.3	50.0	41.4	1.7	50.0	$P<0.01$	B>T B>N
Total-C (mg/dl)	174.0	7.1	158.0	184.4	9.4	169.0	180.4	7.4	189.0	192.4	7.7	141.0	NS	
Total-C/HDL-C	3.7	0.4	2.9	4.1	0.6	3.1	4.4	0.5	3.8	5.2	0.9	2.8	$P<0.05$	T<N B<N
Triglyceride (mg/dl)	99.1	7.4	124.0	137.9	13.9	72.0	104.6	6.6	73.0	108.5	4.5	67.0	NS	

Analyses of the treatment effects and the source of significance were by the randomized block design statistic and the Tukey HSD test, respectively; $n=8$. See text for explanation.

* Analyses for the entire group (G) of subjects.

† Individual values for the female (F) subject.

It is widely believed that androgen therapy increases aggressive behavior in athletes (43, 167). Indeed, the suggestion has been made that the primary beneficial effect on athletic performance is at the level of motivation or aggressiveness (168). If this were in fact a significant phenomenon one would expect the effects to be consistent in the double blind studies of performance whereas such effects are in fact inconsistent. Interestingly, despite widespread belief to the contrary (169), testosterone has no demonstrable effect on behavior in horses (170).

What does all this amount to? It is clear that the potential long term toxic effects are real, but in adult men androgen abuse is not as dangerous as most forms of drug abuse. Both the virilizing and feminizing side effects are largely or completely reversible when the agents are discontinued, really serious hepatic effects are unusual, and the long term consequences of the HDL-C changes are uncertain. Nevertheless, conclusions by some that the agents are safe for athletes are not based on systematic studies of hepatic and gonadal function (53). What is clearly needed is long term followups of athletes who have abused androgens over a long period; such studies are now in progress (171).

CAN ANDROGEN ABUSE BE DETECTED?

The emphasis among athletic organizations clearly has shifted from educating athletes about the dangers of androgen abuse to coercion based upon the detection of their abuse by analysis of body fluids and then disallowing such athletes to compete (172). Different means have to be devised to detect the abuse of normal physiological steroids themselves such as testosterone as compared to use of the various synthetic steroids. Furthermore, the design of tests for the latter agents is complicated by the variability in the dosages of the androgens abused, their unique structures and metabolites, and their differing turnover rates in body compartments, depending both on the degradation rates of the agents and their modes of administration (in general oral agents turn over more quickly than injected agents). One such approach involved radioimmunoassay procedures developed by obtaining antibodies to specific drugs so that relatively specific tests were developed for individual drugs or drug classes (173-175). But at best these assays in fact lack sufficient sensitivity and specificity to be able to detect most users (174). Ultimately, the techniques that have been successful for this purpose are based upon a combination of gas-liquid chromatography and mass spectroscopy of urine (176-183). Namely, suspicious peaks are identified by gas chromatography (Table 6 and Figure 11) and confirmed by mass spectroscopy (Figure 12). Under the sponsorship of the Medical Commission of the International Olympics Committee more and more sophisticated techniques were applied for this purpose at the 1972 and 1976 Olympic games, and by the time of the 1984 games in Los Angeles such testing had become very sophisticated indeed (4, 184). It is of interest that similar tests are now also used to detect the doping of race horses with androgens (185).

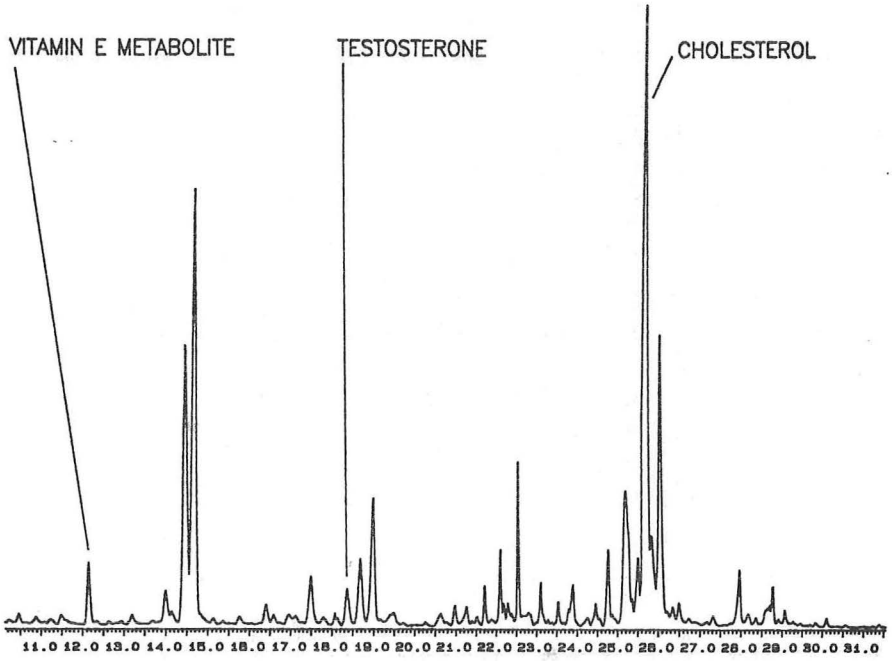

Figure 11: Typical gas chromatogram of a urine extract (From Ref. 184).

Table 6 Retention times of androgenic anabolic steroids (From Ref. 184).

RELATIVE RETENTION TIMES*	COMPOUND
0.67	nandrolone TMS† (metabolite)
0.93	methyltestosterone TMS (metabolite)
0.98	boldenone TMS
0.98	mesterolone TMS
1.00	testosterone TMS
1.04	clostebol TMS
1.05	methenolone TMS
1.15	bolasterone TMS
1.12	methandienone TMS
1.21	norethandrolone TMS (metabolite)
1.25	oxymetholone TMS (metabolite)
1.28	fluoxymesterone TMS
1.28	oxymesterone TMS
1.31	dehydrochlormethyltestosterone TMS (metabolite)

*Retention time of compound ÷ retention time of d_2-testosterone
†TMS = trimethylsilyl derivative

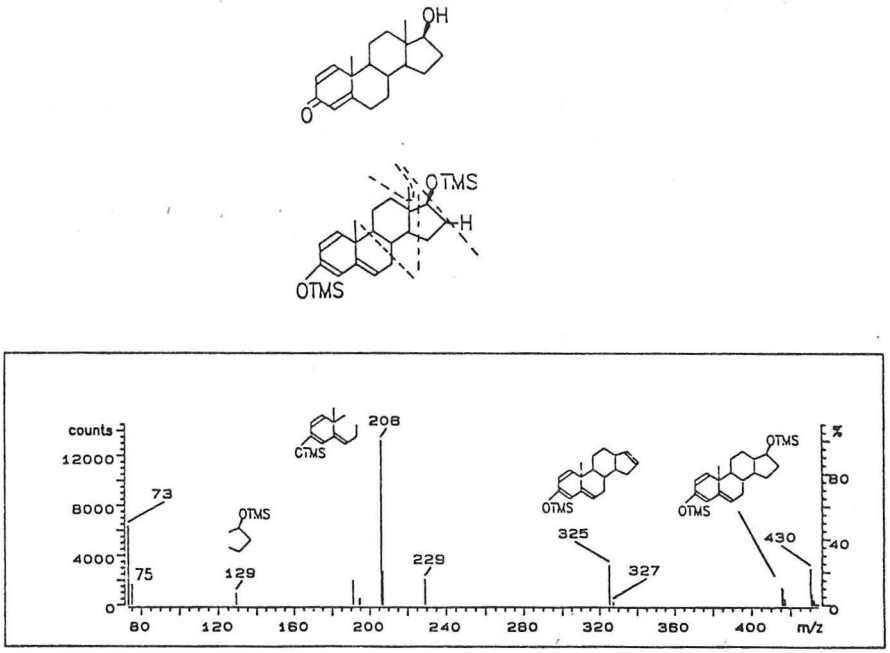

Figure 12: Mass spectrum of the trimethyl sulfate of Boldenone (From Ref. 184).

The underlying principle of such tests is based upon the fact that the altered or impeded steroid molecules are not found in nature, and as a consequence either the parent compounds or unique metabolites can be detected in urine for long periods after their administration. While interfering substances in urine sometimes cause troubles with background readings (180) the sensitivity of such techniques is such that as little as one part of anabolic steroid per billion parts of urine can be detected (183). The net consequence is that with appropriate techniques abuse of any of thirteen or more androgen steroids can be detected in a single assay procedure, the presence of any such metabolites being prima facia evidence of prior drug ingestion (4, 184). A contract was subsequently executed between the Olympic Committee and the University of California at Los Angeles to set up a state-of-the-art analytical laboratory at UCLA for the detection of the abuse of many drugs including androgens. These methodologies were applied at the 1984 Olympic games in Los Angeles for the analysis of urine samples for anabolic steroids are now being utilized for many sports events including post season college football games. The quantity control for the collection and custody of samples, the mechanisms used for screening such samples for suspicious metabolites, the confirmation procedures used to confirm positive results, and the safety margins adapted for the interpretation of borderline assays have been described in detail and provide assurance that the assays are sensitive, specific, and correct (4, 184). It is exceedingly unlikely with such a testing procedure that a false positive could result. At the Los Angeles games 12 of 1510 urine samples examined contained an anabolic steroid.

The detection of the abuse of testosterone esters is not so easy. The esters themselves are split in the body, and the testosterone that is released is metabolized by a similar pathway as the endogenous hormone so that no unique metabolites are excreted in urine. Furthermore, physical training in and of

itself may elevate plasma testosterone levels (186, 187). One method proposed to get around this problem takes advantage of the fact that exogenous testosterone suppresses the secretion of LH by the pituitary and hence alters the normal ratio of LH to testosterone in plasma (188). However, the technique that has been most widely utilized involves the measurement of the ratio in urine of testosterone to epitestosterone, an endogenous C-19 steroid that is not an effective androgen. Donike and his colleagues reported that exogenous testosterone is not epimerized to epitestosterone, that the normal ratio of the two steroids in urine is about 1:1, and that the ratio of testosterone to epitestosterone in urine increases when exogenous testosterone is administered (189) (Fig. 13). Subsequently this assay has been adopted as the means of detection of the abuse of testosterone esters; at the Los Angeles games the testosterone to epitestosterone ratio exceeded 6:1 in 5 of the 1510 urines analyzed (4, 184). However, if one considered the group of athletes in which androgen abuse is most common, namely those that require great strength or weight, abnormal ratios were found in approximately 5% of samples (190). The details of the quality assurance studies establishing that the 6:1 ratio is in fact a valid cutoff point have not been published in detail, but in a survey of approximately 1000 control urines Dr. Catlin found only one urine in which the ratio was ever close to this value (personal communication).

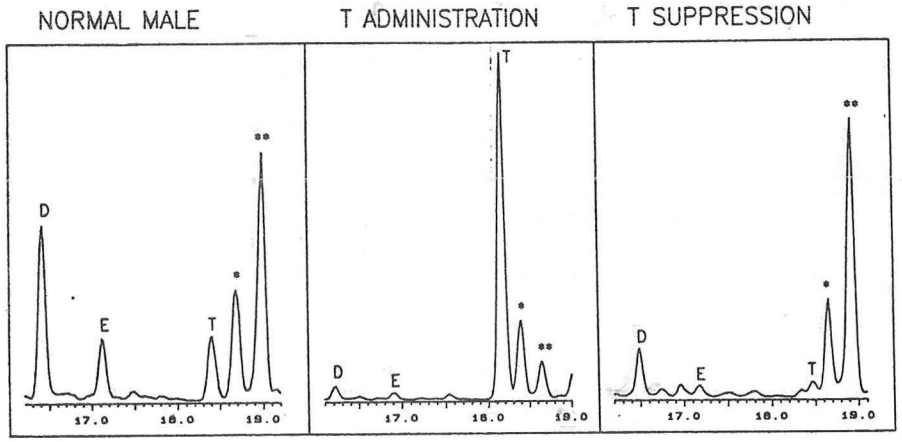

Figure 13: Gas chromatography profiles of endogenous steroids in urine. (T=testosterone, E=epitestosterone) (From Ref. 184).

My conclusion is that these tests as performed at UCLA are accurate in the sense that false positives are exceedingly rare. Furthermore, in instances of abuse of steriods that are excreted slowly from the body, as for example the administration of decadurabolin athletes can be identified who have taken the agents in the remote past (say 6-9 months previously). Whether the incidence of false negatives is equally low is not so clear. Namely, the issue as to whether the tests are fair, specifically establishing the percentage of androgen abusers that are detected, simply has not been established. That is, no groups have been studied in which abuse of the various drugs drugs was stopped at a given time and it was subsequently determined how long it takes for washout of the various agents to take place.

Intuitively it seems obvious that there must be wide variability in the rates at which the various drugs are cleared, and it is possible that some of

the various techniques that have been devised to promote "washout", including benemide ingestion, may in fact serve to mask prior use of the drugs. Until these various issues are resolved, it will not be clear whether the elaborate urine testing procedures do in fact detect more than a fraction of abusers of the drug. On the one hand, the fact that only a small percentage of the urine tested at the Los Angeles games were positive could mean that androgen abuse is in fact decreasing, or, alternatively, it may mean that the majority of abusers have succeeded in masking their use.

CONCLUSIONS

This is one of those subjects on the border between medical science and sociology for which there can be no definitive value judgment. At the scientific level it is almost certain, although unproven, that androgens do promote muscle growth and strength in women and in adolescents of both sexes, and it is likely that this phenomenon, like the sexual dimorphism of his muscle development, is mediated by androgen acting through the androgen receptor. At the same time it is not so clear whether androgens have a beneficial effect of any type in male athletes, and if they do it is not certain how they work.

On the negative side, the side effects are worse in those groups - women and children - who might benefit most and hence preclude their use by any but a fanatic subset of women athletes (191). The virilizing and feminizing side effects in men are largely reversible, and it is not known whether the toxic side effects, and in particular the long term toxic side effects, are mitigated by intermittent use of the agents. On balance, however, the side effects are such as to preclude their use on medical grounds.

How best to prevent their use is not established. The various official sports organizations have established their programs of drug detection and enforcement on the assumption that they do work and hence that their abuse provides an unfair advantage as well as upon an assumption that the toxic side effects are significant. Whether the drug testing program does discourage androgen abuse or whether it has been effectively circumvented is not clear.

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