THE USE OF PERFORMANCING DRUGS IN COMPETITIVE ATHLETICS. WHAT IS TO BE DONE?

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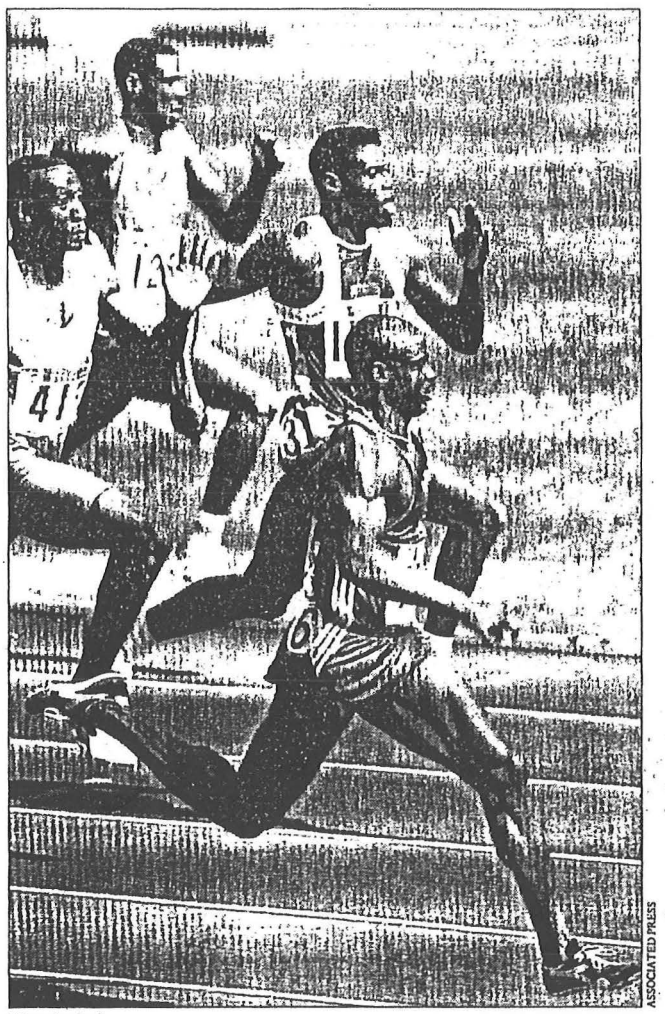

What price glory?

Jean D. Wilson has no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

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- Androgen physiology and the mechanism of action of androgens
- Sexual differentiation and the disorders of human intersex

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Introduction

Although a byproduct of modern pharmacology, the use of performance enhancing drugs in competitive athletics is a problem of society rather than a medical issue.. However, physicians are involved in the study and use of these agents in athletes and in the effort to contain an epidemic, the seriousness of which has been underestimated in the past and which appears to be worsening. Use of these agents is equally or more common among body builders, but since body building is not controlled in the same way as competitive athletics the use for this purpose will not be discussed.

Because of widespread recognition that the use of performance enhancers is poisoning competitive athletics and because the US Olympic Organization and its Medical Advisory Committee have been the subject of widespread criticism in this country and abroad for ineffectiveness, responsibility for dealing with performance enhancing drugs has been removed from the control of the sports federations in this country and transferred to a new federal bureau, the United States Anti-doping Agency (USADA). This agency, modeled in several ways on the Canadian Centre for Ethics in Sports, is in the process of organizing and formulating a comprehensive agenda, and this is an appropriate moment to review the problems that are faced. A variety of agents are prohibited by the Olympic Movement, some under all circumstances and others conditionally. (Table 1)

TABLE 1. OLYMPIC MOVEMENT PROHIBITIONS (2000)

PROHIBITED UNDER ALL CONDITIONS

- STIMULANTS
- NARCOTICS
- BETA-2 AGONISTS
- DIURETICS
- PEPTIDE HORMONES, MIMETICS, AND ANALOGUES
- ANDROGENS

PROHIBITED IN SOME CIRCUMSTANCES

- ALCOHOL
- LOCAL ANESTHETICS
- BETA-BLOCKERS
- CANNABOIDS
- GLUCOCORTICOIDS

PROHIBITED METHODS

- BLOOD DOPING
- ARTIFICIAL OXYGEN CARRIERS OR PLASMA EXPANDERS
- PHARMACOLOGICAL, CHEMICAL, AND PHYSICAL MANIPULATION

Table 2. MOST COMMON BANNED DRUGS USED FOR PERFORMANCE ENHANCEMENT, 2000

STIMULANTS

Amineptine	Caffeine	Fencamfamin	Salbutamol
Amiphenazole	Carphedon	Mesocarb	Salmeterol
Amphetamines	Cocaine	Pentetrazol	Terbutaline
Bromatan	Ephedrines	Pipradol	

...and 35 related substances

NARCOTICS

Buprenorphine	Heroin	Morphine	Pethidine
Dextromoramide	Methadone	Pentazocine	Hydrocodone

...and related substances

BETA-2 AGONISTS

Bambuterol	Fenoterol	Reproterol	Terbutaline
Clenbuterol	Formoterol	Salbutamol	

...and related substances

DIURETICS

Acetazolamide	Ethacrynic Acid	Mannitol	Triamterine
Bumetanide	Furosemide	Mersalyl	Bendroflumethiazide
Chlortalidone	Hydrochlorthiazide	Spironolactone	Indapamide
Canrenone			

...and related substances

PEPTIDE HORMONES, MIMETICS, AND ANALOGUES

Gonadotropins	Growth hormone	Erythropoietin
Corticotropins	IGF-1	Insulin (except diabetics)

...and all releasing factors and their analogues

ANDROGENIC STEROIDS

Androstenediol	Dihydrotestosterone	Nandrolone	Stanozolol
Androstenedione	Fluoxymesterone	19-Norandrostenediol	Testosterone
Clostebol	Metandienone	19-Norandrostenedione	Epitestosterone
DHEA	Metenolone	Oxandrolone	Boldenone

...and more than 16 related substances

BETA BLOCKERS

Acebutolol	Bunolol	Levobunolol	Pindolol
Alprenolol	Carteolol	Metipranolol	Popranolol
Atenolol	Celiprolol	Metropranol	Sotalol
Betaxolol	Esmolol	Nadolol	Timolol
Bisoprolol	Labetalol	Oxyprenolol	

...and related substances

Some drugs can be taken under medical supervision (inhaled beta-agonists by asthmatics and insulin by documented diabetics). Others are prohibited only for some sports, as exemplified by the banning of β-blockers only for sports involving marksmanship. At the time of the 2000 games in Sydney more than 150 individual drugs were on the prohibited list, the most common ones being listed in Table 2. Use of *narcotics* is banned, not because of any putative enhancement of performance but because of potential danger to the athletes taking them. *Diuretics* are taken by athletes to qualify for specific weight categories of competition. Consequently, they are not performance enhancers but rather performance qualifying agents. Their use can predispose to volume depletion and its complications, particularly in those events in which only a short time is allowed between weigh-in and competition (1). The remainder of the agents are banned because of the belief that they are used to enhance performance.

Banned Drugs of Doubtful Efficacy

There is considerable variability in the quality and depth with the performance enhancing abilities of the various banned agents; these various studies have been the subject of detailed reviews (1,2). Because of variability in study design, controls employed, the use of trained versus untrained subjects, and numbers of subjects in each study, all negative data must be interpreted cautiously. All one can conclude is that the evidence either supports or does not support efficacy, and it is worthwhile remembering in this regard that it required many years of study to establish that supraphysiological doses of androgen enhance muscle growth and strength (3).

Stimulants Amphetamines and strychnine were apparently the first drugs in modern times to be used for the purpose of performance enhancement, namely by bicyclists in the 1930s, and amphetamine use is believed to have led to the death of a cyclist in the 1960 Olympic games and of a competitor in the 1968 Tour de France. (2). The performance enhancing effects of only three types of stimulants appear to have been studied, *amphetamines* and *ephedrine* in some depth and *cocaine* to a limited extent. In all three evidence for a beneficial effect on athletic performance is inconsistent, equivocal, and unconvincing. Smith and Beecher originally reported that performance was enhanced by amphetamine sulfate in 77 percent of runners, swimmers, and discus throwers (4), but most subsequent studies that were blinded appropriately have failed to demonstrate beneficial effects, and most reviewers have concluded that these agents at best mask pain and fatigue but do not improve endurance and sometimes work to the detriment of the athlete, as for example causing them to ignore injuries (1).

Growth hormone and its mimetics Anecdotal reports of athletes using human growth hormone began to appear in the early eighties, and with the release of recombinant human growth hormone rumors of use by athletes increased and lead to hearings by the US House of Representatives and to a study by the General Accounting Office, both of which concluded that very little human growth hormone is available on the black marked and that the expense of the drug limits its potential for abuse (2). Some of what is sold as human growth hormone is in fact either bovine growth hormone or primate hormone, but

despite great care by the manufacturers some of the street drug is recombinant human growth hormone.

The rationale behind growth hormone use is foggy because the muscles of acromegalics and pituitary giants are weak. However, administration of growth hormone to growth hormone deficient individuals enhances nitrogen retention, and the administration of 8 mg/week to well trained normal adults decreases the percentage of body fat and increases fat-free mass (5). The question is what fat-free compartment is being enhanced? In double-blind, placebo-controlled studies, treatment of male power athletes (6) or untrained individuals (7) with somewhat lower doses of human growth hormone did not change muscle strength, body or weight or body fat. Likewise, there is no effect of hGH on whole body protein synthesis or on skeletal muscle protein in weight lifters (8). Infact, the retained nitrogen appears to be deposited in bone and connective tissue (9).

At any rate, there is no evidence that growth hormone enhances athlethic performance, and it is assumed that the same unc ertainty applies to *IGF 1* and to *growth hormone mimetics* and *stimulants*. Whatever the merits of the case, it is likely for the foreseeable future that the abuse of growth hormone and its mimetics will be limited because of the great expense involved. *Insulin*, the street name of which is "the real stuff," is taken by body builders with the belief that it is the most effective anabolic agent of all. It is taken after workouts (8-10 units of regular insulin) followed by the injestion of a large meal. There are no studies of its effects in this regard, but its use might improve anabolism.

Banned Drugs of Established Efficacy

Beta blockers *β-Adrenergic blockers* reduce heart rate, decrease cardiac output, and reduce maximum oxygen consumption (10) and adversely affect endurance and time of running, and presumably other aerobic sports (1). Most studies of these agents were done using relatively non-selective inhibitors, but both propranolol and metoprolol decrease the capacity to exercise (11). Consequently, they are not used by most athletes. However, β-blockers are thought to be effective reducing tremor and heart rate in sports that require precision and in which physical performance is not rate limiting, namely diving, archery, shooting, and ski jumping (2). In interpreting the literature on this phenomenon it is essential that all studies be appropriately blinded because there is a very large placebo effect (12). In a well designed study, Kruse et al reported that the administration of metroprolol to marksmen prior to shooting improved performance by an average of 13 percent (13). (Figure 1) In regard to marksmanship, the original assumption was that slowing the heart rate made it possible to time pulling the trigger to diastole, thus preventing the disruptive effects of cardioballistic vibrations. Although there was a clear decrease in average heart rate, the lack of correlation between improved marksmanship and change in heart rate lead Kruse et al to conclude that the principal effect was to reduce hand tremor (13). Other studies have reported similar improvement in shooting performance while taking ocyprenolol (14,15). The interpretation that the effect is primarily to reduce hand tremor is in keeping with the evidence presented by Larsson and Svedmyr (16) and by Abila et al (17) that catecholamines induce tremor by stimulating β-receptors in skeletal muscle.

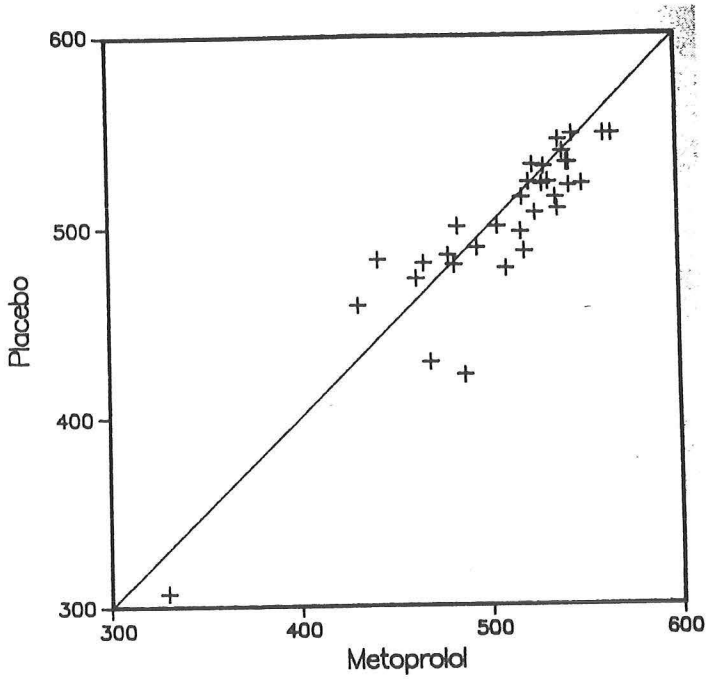

FIG. 1. Plot of metoprolol vs. placebo shooting points. Line of identity is drawn solid to a theoretical maximum (600,600).

Because β-blockers have to be taken on the day of competition it is likely that most urinary testing procedures are effective, and the fact that the number of positive urine tests in random screens of competitors declined after such testing became standard (2) has led most to conclude that the use of these agents is under control and is not currently a major problem in competitive sports. It is of interest, nevertheless, that a technique has been developed for the detection of both β2-agonists and β-blockers in single human hairs using GC/MS, and it clear that chronic use of these agents can be detected with this procedure (18). The limits of detection, namely how many days the drug must be taken to be detected, and whether it actually adds any new capability to the current urine tests have not been established.

Enhancement of Erythropoiesis The oxygen-carrying capacity of blood increases with increases in red cell mass, which can be induced either by transfusion or by the administration of erythropoietin. One technique, so called "blood doping," involves phlebotomy, freezing the red cells, allowing 8 to 12 weeks for recovery of the hematocrit, and reinfusion of the red cells 1 to 2 days before the event. Most information in this arena is anecdotal, but it is believed that 7 of 24 cyclists on the 1984 US Olympic Team (four of whom won medals) received homologous blood transfusions (2). The capacity for aerobic exercise depends on oxygen delivery and the ability of muscles to use oxygen, and which of the two limits exercise capacity is not always clear. The fact that maximal aerobic power correlates with red cell mass has suggested that under ordinary circumstances oxygen carrying capacity is rate-limiting (19), but other theories about the increase in exercise capacity include increased cardiac output as the result of expanded blood volume, improved buffering capacity for lactic acid, and enhanced heat dissipation. At any rate, administration of homologous transfusions to highly trained athletes caused significant increases in hemoglobin levels, maximal oxygen uptake, and endurance (20,21). The same effect is achieved with autologous transfusions, but it is of interest that increased exercise endurance does not correlate with the magnitude of increase in maximal oxygen uptake but is instead a function of the individual's initial aerobic fitness

(22). Homologous blood transfusions are detectable by immunologic tests, but there is no practical means for detecting autologous transfusions, largely because of the wide range of hemoglobin levels among athletes. Autologous transfusion is believed to be a limited or rare procedure because it requires trained accomplices and a -70^{o} freezer.

Administration of erythropoietin has similar effects in that over a 7 to 8 week period it increases the hematocrit of normal men about 10 percent (23). The increase in hematocrit is accompanied by an increase in maximal oxygen uptake of 8 to 10 percent, an effect that is lost within weeks after discontinuing the drug (24). (Figure 2). The increased exercise performance is accompanied by a decrease in the accumulation of hypoxanthine and lactate in blood (25). (Figure 3) This regimen is not without risk. Adamson and

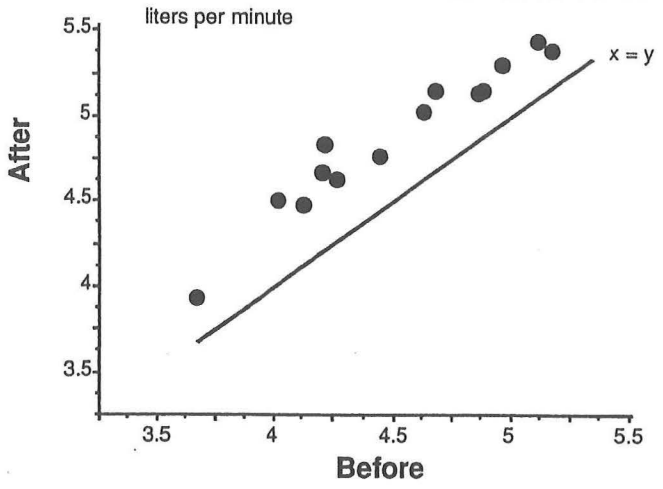

Figure 2. Maximal aerobic power (liters per minute) before and after 6 to 7 weeks of EPO administration. (24)

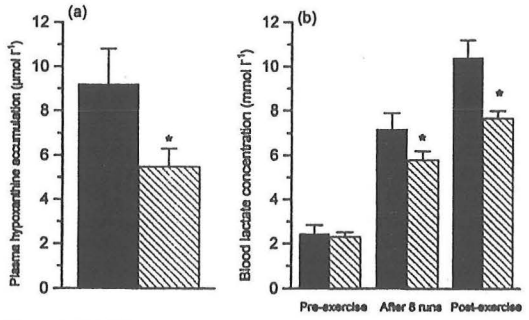

Fig. 1. (a) Plasma hypoxanthine accumulation [post- (13.3 (1.8) and 12.7 (1.6)) minus pre-(4.2 (0.4) and 7.1 (0.9) μmol l^{-1}) concentration] and (b) blood lactate concentration for the intermittent exercise protocol before ■ and after ▨ the administration period (mean and SEM, $n = 6$: * after significantly different from before). (25)

Vapnek pointed out that the effect of the drug may continue for several days after it is discontinued so that there is the potential of overshooting the hematocrit (26), a worrisome issue since the rare adverse effects of the drug (thrombotic events, seizures, and hypertension) are presumed to be secondary to expanded blood volume and increased blood viscosity (27,28). Of greater worry in athletes is the fact that although erythropoietin does not change basal blood pressure levels in normal men, exercise-induced increase in blood pressure is markedly enhanced by erythropoietin (29), and even in athletes there may be an increased risk for intravascular coagulation (23).

The magnitude of erythropoietin abuse is not clear because the drug has a very rapid half life in plasma and in urine, but 14 of 102 samples from participants in the 1999 Tour de France had recombinant human growth hormone in the urine, indicating that the drug in these individuals had been taken within the previous day or so (30). The fact that mean hemoglobin levels in elite cross-country skiers continued to increase between 1987 and 1999 also suggests that the use of artificial means of increasing hemoglobin levels is widespread (31), It is of interest in this regard that the organizers of the Sydney Olympics

announced that a valid assay for recombinant erythropoietin would be available for the 2000 games (as it turned out suitable control studies were not completed in time and the assay was not used). Just after this announcement one country mysteriously withdrew 300 athletes from competition (and cancelled one chartered jet) so that there is the general belief among the relevant agencies that use of this agent is widespread.

β2-Agonists β2-agonists are used extensively in meat-production to decrease the fat content and increase muscle mass, the mechanism for these effects never having been established (32), and the drug was detected in the urine of athletes first in 1992 Summer Olympics (33). The administration of clenbuterol to patients recovering from surgery caused a more rapid recovery of strength in the knee extensor muscles (34), and the administration of salbutamol (but not placebo) to 12 healthy men (not trained athletes) increased strength in the hamstring and quadriceps strength on average between 10 and 15 percent but had no effect on handgrip, body weight, skinfold thickness, or limb circumference (35).

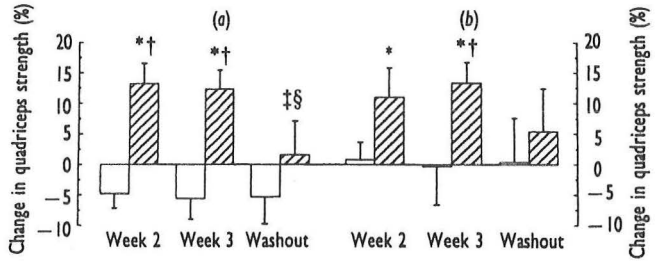

Fig. 1. Changes in strength of the quadriceps of the dominant (*a*) and non-dominant (*b*) leg (means ±SEM) after ingestion of either placebo (□) or salbutamol (▨) for 2 and 3 weeks, and after a 4-week washout period. Statistical significance: *$P<0.05$ compared with baseline; †$P<0.05$ compared with placebo; ‡$P<0.05$ compared with week 2; §$P<0.05$ compared with week 3.

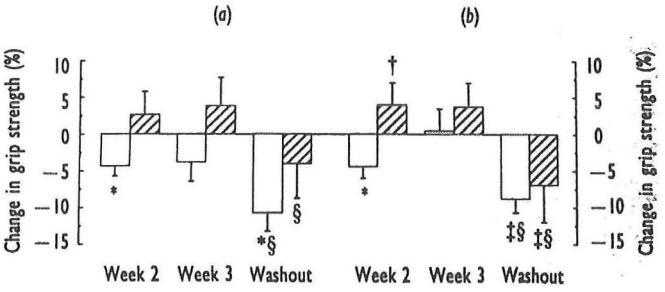

Fig. 3. Changes in grip strength of the dominant (*a*) and non-dominant (*b*) hand (means ±SEM) after ingestion of either placebo (□) or salbutamol (▨) for 2 and 3 weeks, and after a 4-week washout period. Statistical significance: *$P<0.05$ compared with baseline; †$P<0.05$ compared with placebo; ‡$P<0.05$ compared with week 2; §$P<0.05$ compared with week 3.

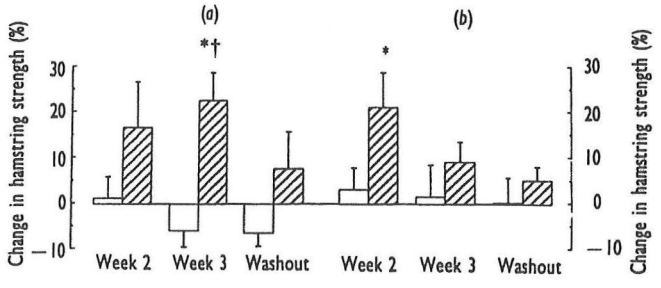

Fig. 2. Changes in strength of the hamstring of the dominant (*a*) and non-dominant (*b*) leg (means ±SEM) after ingestion of either placebo (□) or salbutamol (▨) for 2 and 3 weeks, and after a 4-week washout period. Statistical significance: *$P<0.05$ compared with baseline; †$P<0.05$ compared with placebo.

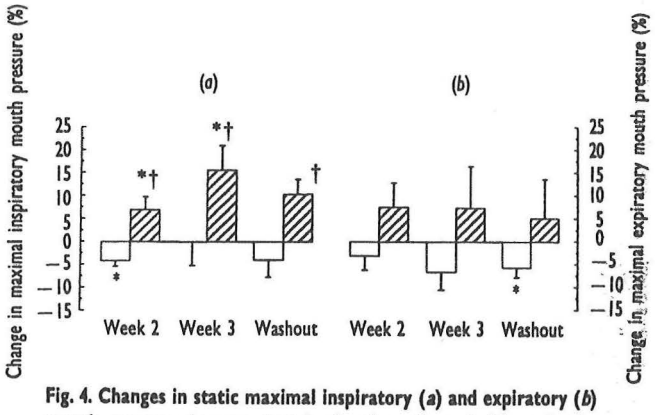

Fig. 4. Changes in static maximal inspiratory (*a*) and expiratory (*b*) mouth pressure (means ±SEM) after ingestion of either placebo (□) or salbutamol (▨) for 2 and 3 weeks, and after a 4-week washout period. Statistical significance: *$P<0.05$ compared with baseline; †$P<0.05$ compared with placebo. (35)

Likewise, administration of albuterol during a strength-training program increased most measures of strength (36). Whether the acute inhalation of these agents as aerosols influences athlethic performance in non-asthmatic trained, elite athletes is not clear, some studies reporting no effects (37,38) and some showing short-term effects on ergogenic output (39,40). The use of these agents can be detected both in urine and in hair (18), and it appears that it is possible to discriminate between the use of the oral and inhaled medicines (41). However, the time sequence of reversibility of the positive effects on strength have not been defined, and it is not clear whether urine detection methods are effective in practice.

This brings us to androgens, the most effective and widely used performance-enhancing drugs.

Androgens

Androgen abuse by athletes has been the subject of several reviews (42-45), and it is beyond the scope of today's lecture to review the subject in detail. The rationale for their use stemmed from two observations--that androgen replacement in hypogonadal men increases muscle mass and that the differences in muscle development between men and women (largely the limb girdle muscles) are androgen mediated. Use in athletes stemmed from the extension of the "cold war" to international sports competition. A widely accepted account is that John B. Ziegler, a physician for the U. S. weight lifting team, was told by a Russian team physician at the 1954 world championship meet in Vienna that some members of the Russian team used androgens. Ziegler assumed that androgens would enhance athletic performance, and he persuaded the Ciba corporation to let him experiment with methandrostenolol, and oral androgen. Most studies that he and others did (using relatively modest doses of the drug) did not show any clear effect on strength or performance (42) and Ziegler himself concluded that the effects of the drug were purely psychological. Regardless of the evidence, athletes and trainers believed that androgens enhance performance, and their use (in much larger doses than had been studied by exercise physiologists) spread through a variety of sports, professional and amateur, involving men and women, and even to the high school and junior high school levels. This epidemic is worldwide and has occurred despite the attempts of sports organizations to discourage the practice so that by the 1964 Olympics androgen use was widespread among competitors, most importantly in those events directly dependent on weight or strength. For example, all the weight lifters in the 1968 U.S. training camp had taken androgens (46), and 68 percent of the runners interviewed at the 1972 Olympics had taken the agents in preparation for the games (42.) Androgens have been on the list of banned drugs for Olympic competition since 1976.

What are androgens? Testosterone, the principal androgen secreted by the testes, cannot be administered either by mouth or by injection. Oral administration is followed by absorption into the portal circulation and first pass removal by the liver so that only trivial amounts reach the systemic circulation, and the hormone is rapidly absorbed after parenteral administration and turned over rapidly so that effective plasma levels are not

sustained. Therefore, the molecule has to be modified to circumvent these problems, and the most useful alterations can be categorized into three types:

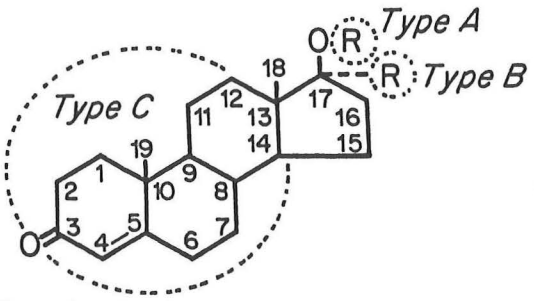

FIG. 1. Categories of androgens commonly used pharmacologically. Type A, esterfied androgens; type B, 17-alkylated androgens; type C, androgens with alterations of the steroid nucleus.

1.) Esterification at the 17 position with various carboxylic acids decreases the polarity of the steroid, making it more soluble in the vehicles used for injection and hence slowing release of the hormone into the circulation. Esterified androgens must be hydrolyzed prior to action, and the effectiveness of therapy can be monitored by assessing the plasma tesosterone by immunoassay; 2.) Alkylation at the 17α-position (or in the one position) with either a methyl or ethyl group inhibits hepatic metabolism and makes the compound orally effective. Because there is no known mechanism for removing the alkyl group unique metabolites are present in the blood and urine after administration; 3.) Alterations of the ring structure are common in both oral agents and parenteral formulations. They may slow the inactivation, enhance the potency of a given molecule, or alter its metabolism (for example, by precluding conversion to estrogens). These various agents are excreted as unique metabolites, and, like the alkyl derivatives, it is this aspect of their pharmacology that makes it possible to detect their use by athletes.

All androgens have both androgenic and anabolic actions, and virtually all can be effective in the treatment of hypogonadism, effects that are mediated through a single receptor protein.

Do Androgens Work in Normal Men and, if so, How do they Work? In pharmacological dosages androgens do increase body mass and strenngth, but proving this turned out to be surprisingly difficult for two reasons: 1.) A major placebo effect was demonstrated in a famous study by Ariel and Saville in a group of athletes undergoing weight training at the University of Massachusetts; these individuals were told that the best among the group would be given methandrostenolone but were instead given a placebo, which caused an accelerated rate of improvement (47). As a consequence it is necessary to blind studies of efficacy, which is not easy to do because side effects such as acne can give away who is getting real drug. 2.) The dosages that are actually used by athletes are higher than most human experimentation committees will approve for studies in normal people. For this reason it is not possible to extrapolate established toxicological and pharmacological data to athletes. This issue can be illustrated by the situation in regard to methandrostenolone,

the most widely used androgen preparation in this country in the early days of the epidemic. Liddle and Burke showed that 1.25-2.50 mg/d causes maximal nitrogen retention in hypogonadal men (48), and initially it was thought that most athletes took 10-20 mg/d, and studies of the effects of the drug on athletic performance utilized this dose range, which was after all 10-15 times the physiological dose. Whether these doses ever had any relation to the actual pattern of abuse is moot, because in fact androgens are taken in much larger amounts.

In one study, 110 of 250 weight lifters in a single gym admitted androgen abuse, commonly involving a so-called "stacked pyramid" involving increasing dosages of multiple oral and parenteral agents prior to athletic events, frequently followed by washout periods (49). The same pattern of administration is common in Europe (50) as illustrated:

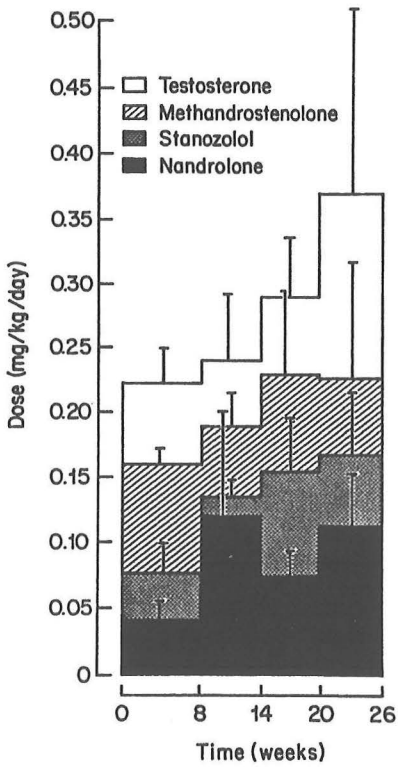

FIG. 3. An example of a stacked pyramid of androgen self-administration by one group of power athletes in Finland. The mean daily doses ± SEM of self-administered androgens are shown. [Reproduced with permission from M. Alen *et al.*: *Med Sci Sports Exerc* 17:354, 1985(48).]

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These doses are 10 to 100 times the levels used in most studies of toxicology and pharmacology and several times the levels that were tested originally in athletes. Whatever the scientific evidence, coaches and trainers believed that they were having an effect and that the accelerated rate of breaking records correlated with andogen use. One of the pieces of evidence they cited was the fact that the mean weight of the 10 best weight lifters at the annual Norwegian championships increased 18 kg between 1962 and

1982 (51). It was argued that the frequent breaking of records was due to androgen use rather than to improved training and nutrition (52). Solid evidence that these superdoses are in fact effective came from a clever retrospective study by Gilbert Forbes who suggested that the relation between lean body mass and androgen is a function of the total dosage; namely, after administration of about 20 g exogenous androgen lean body weight increases about 18 kg (53). It is fascinating that 20 g is about the amount of testosterone secreted by the human testes to carry boys through puberty (from age 11 to 18) and that the mean difference in lean body mass between men and women is around 18 kg. Forbes et al went on to show that lean body mass does not return to baseline until 150 day after discontinuing these supraphysiological doses (54), a phenomenon that enormously complicates detection schemes.

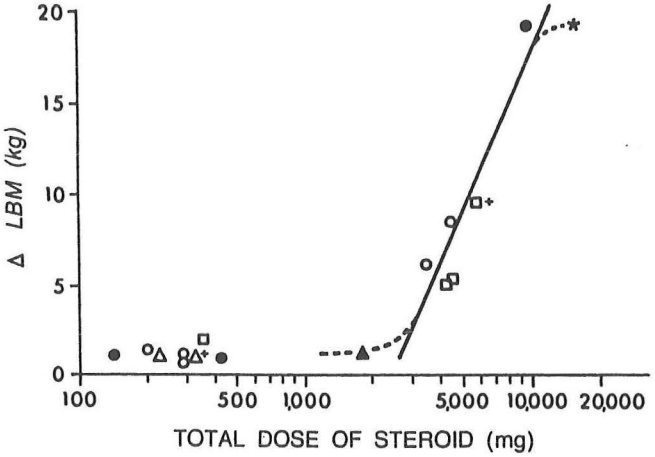
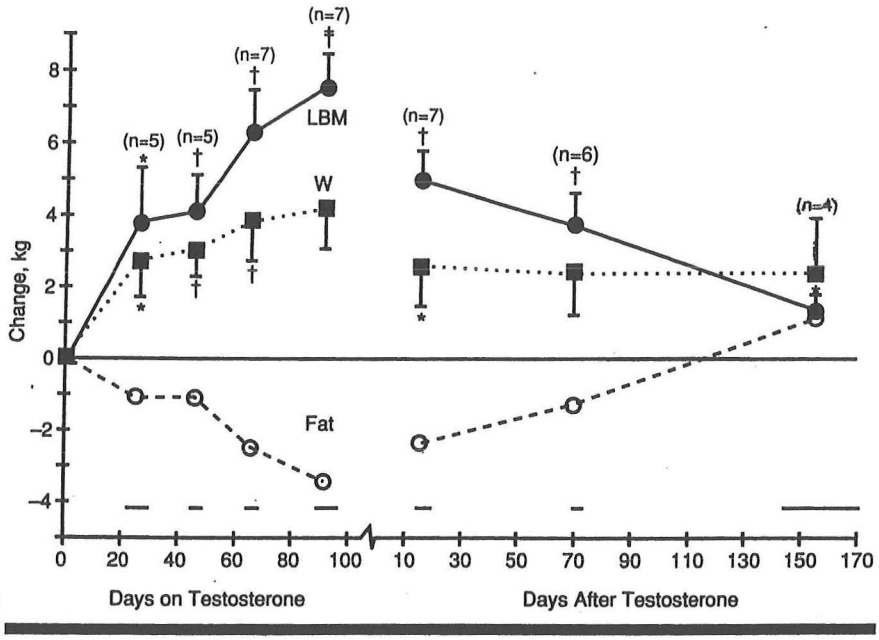


FIG. 5. Semilogarithmic plot of increment in lean body mass against total dose of androgens administered in several different studies. The different symbols represent different androgens. [Reproduced with permission from G. B. Forbes: *Metabolism* 34:571, 1985(90).] (53)



Time course of weight (W) change (dotted lines), lean body mass (LBM) change (solid lines), and body fat change (dashed lines) in response to testosterone administration and following cessation of drug. Time zero for the latter was taken as 21 days after the last testosterone injection. Data given are means ±SEM; number of subjects is shown in parentheses. Statistical significance was determined by one-tailed *t* tests. Horizontal lines at bottom of Figure indicate mean assay intervals ±SEM; asterisks, $P<.05$; daggers, $P<.01$; and double dagger, $P<.001$. (54)

Any remaining doubts about this issue were put to rest by the publication in 1996 of a very careful study by Bhasin and his colleagues of the effects of supraphysiological doses of testosterone on muscle size and strength (3). They administered placebo or testosterone enanthate (600 mg/wk) for 10 weeks to 43 healthy men and showed clear increases in fat free mass, muscle size, and strength, regardless of whether the men exercised during the study period. Athletes, trainers, and coaches were right!

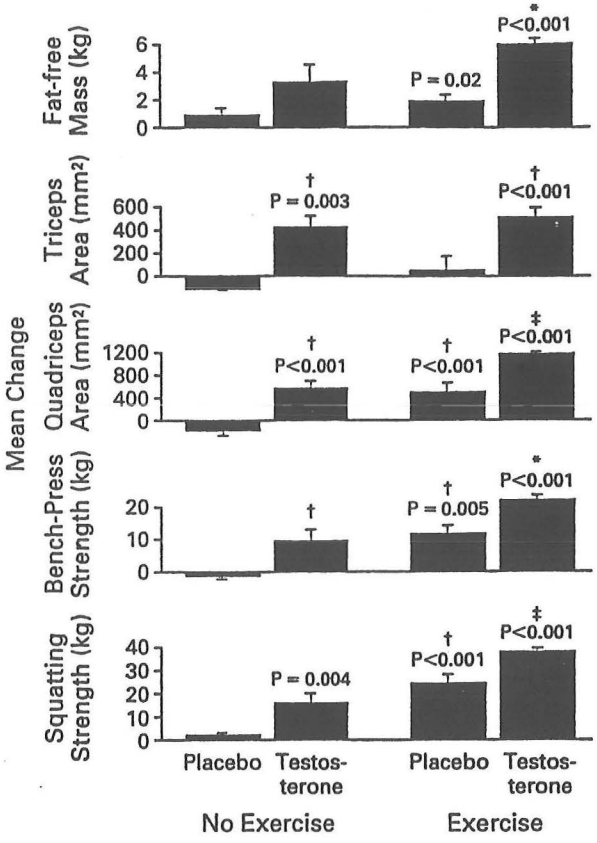


Figure 1. Changes from Base Line in Mean (±SE) Fat-free Mass, Triceps and Quadriceps Cross-Sectional Areas, and Muscle Strength in the Bench-Press and Squatting Exercises over the 10 Weeks of Treatment. (3)

Androgen clearly acts via the androgen receptor to promote sexually dimorphic muscle development in animals (42), and it follows that androgen promotes muscle growth in women by a similar mechanism. However, after puberty men act physiologically as if the androgen receptor is saturated and/or downregulated (42), and how supraphysiological doses promote anabolism in men is at all not clear. One possible explanation is that androgens at high dosage act as antagonists to the catabolic effects of glucocorticoids and hence promote anabolism independent of the androgen receptor (55). If this is indeed the case the effect would be to slow turnover of body protein rather than enhance protein synthesis (56). It is very interesting in this regard that methyltestosterone is an effective competitive inhibitor of the binding triancinolone to the glucocorticoid receptor (57).

In addition, a significant portion of the increase in lean mass is the consequence of expansion of red cell mass, amounting to about 1g/dL increase in the hematocrit and 15 percent increase in blood volume (58), effects presumed to be mediated by an increase in erythropoietin levels (59).

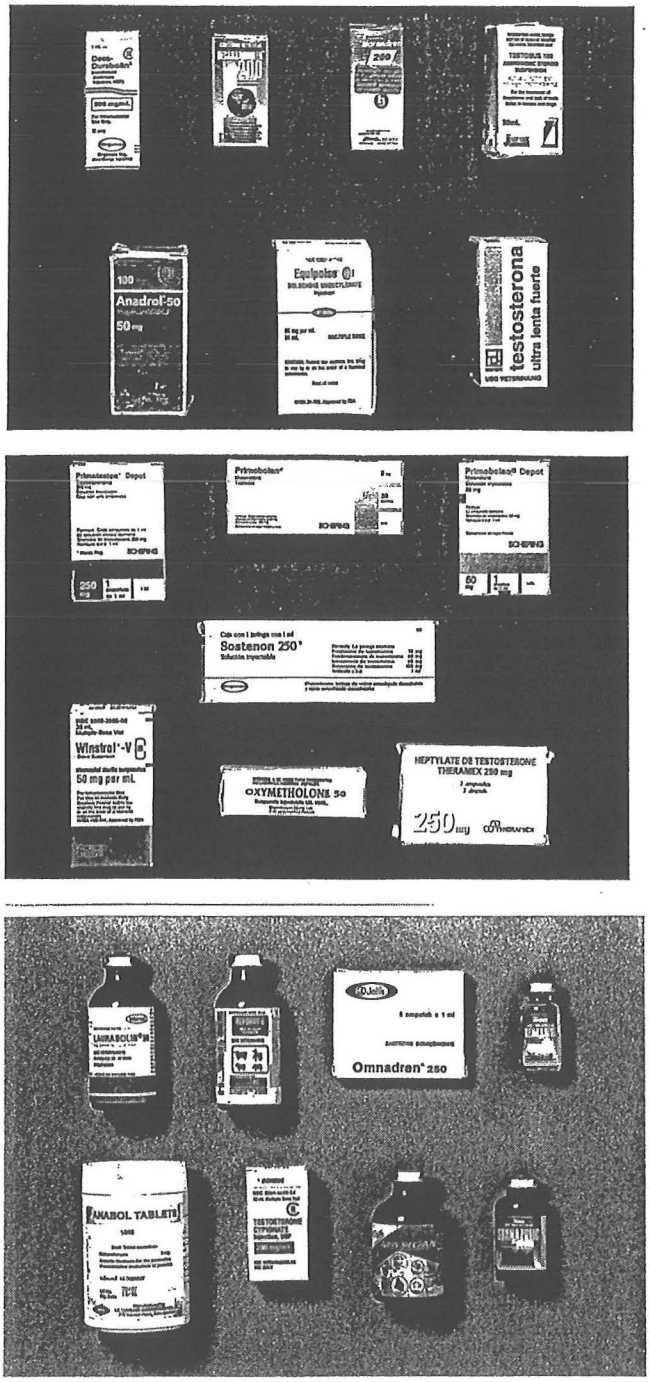
How are Androgens Obtained by Athletes? Here one is dealing in part with hearsay, but fundamentally there are three sources: physicians, the underground, and (in some countries) government agencies.

1.) *Physicians* In one study of the pattern of abuse about a fifth of steroid users obtained them by prescription from physicians (60), a mixture of deluded (or fanatic) sports physicians who believe that they are doing the right thing and physicians of the type described in *The Underground Steroid Handbook* (61):

> Lucky for us though there is a large number of what we call the 'businessman doctor.' These guys are out to hustle a buck. . . . Steroid users are regular, cash paying customers who take up little of a doctor's time. This is financially attractive to him as it frees him to make more money with other patients. Some of the most successful doctors on the West Coast who specialize in steroids have between 1000 and 1500 steroid patients. As you can imagine, this is a very lucrative sideline. You should ask the doctor if he has an interest in building up a steroid clientele as you should be able to pitch him a lot of business. Don't be indiscriminate though; don't send him a deluge of crazies, animals and loudmouths. We've seen that happen before, and what results is suddenly the doctor will not see anyone for steroids. So be careful; don't spoil it for yourself.

Whatever the motivation of the physician, the prescription of androgens for this purpose is unethical and in some countries and in some states in this country illegal.

2.) *The Steroid Underground* The major source of androgens is the black market, which is largely operated by trainers, gymnasium owners, and others on the periphery of sports (62). As is true for other drug undergrounds, the profits made in trade are enormous, and several nationwide networks of traffic in these drugs have been broken up (62). As is also true for other drug undergrounds, the efforts to contain this one appear to have been totally ineffective. The magnitude of this problem is illustrated by a study done by Chris Street, a sports journalist, who last fall persuaded attendees at one gym in Houston to give him their discarded androgen containers and who allowed me to have them photographed:



Keeping in mind that this represents the gleanings from only a few gyms, it is of interest that the 22 different formulations include 19 parenteral and 3 oral formulations, are made by established drug companies (Organon, Pharmacia and Upjohn, Schering) and by manufacturers of unknown provenance (and unknown standards of purity), and are from five countries (the US, Poland, Australia, Mexico, and Thailand). The most striking feature of the collection, however, is that 7 of the 22 containers are marked for veterinary use only. The most commonly abused veterinary drugs are mibolerone, a drug used in

abuse in horse racing), and a parenteral formulation of stanozolol not approved for human use. These agents are not approved for human use in any country become of toxicity, most commonly hepatic toxicity. The most interesting of this collection, however, is methandrostenolone; because of widespread abuse of this drug (under the name dianabol) its manufacture was stopped in this country and then by all subsidiaries of Ciba-Geigy world wide, but it has reappeared on the black market from Thailand. The safety of these black market drugs has not been established, and many are believed to contain unknown or unexpected ingredients. The sharing of needles for the self-administration of parenteral androgens by athletes carries the same risks as needle sharing in other forms of drug abuse, including one case of HIV transmission (63).

3.) *Government-Sanctioned Sources* For many years the rumor circulated that iron-curtain governments systematically used androgens in their sports programs. For the most part, these stories were thought to be cold war paranoia, and consequently it came as something of a shock to western sports organizations when the record of the secret doping program of the German Democratic Republic was published in 1997 (64). In brief, convinced on the basis of systematic administration to athletes prior to the 1972 Olympics that androgens improve athletic performance and having experimented with the use of the agents extensively, a formal government bill was approved in 1974 by the Central Committee of the reigning Socialist party. This bill provided that the administration of doping substances, notably androgenic steroids, should:

- Be an integral part of the training and preparation for competitions
- Be organized tightly and centrally, including evaluations of reports by the sports physicians involved
- Be directly controlled by the government sports agency
- Be developed by further research with emphasis on new substances and development of means to avoid detection at international events.
- Be taught to sports physicians and coaches in formal documents and courses
- Take place in absolute secrecy and be classified as an Official State Secret

The means by which this program was organized and conducted is described in considerable detail, including the administration of the drugs to female athletes under coercion of a variety of types and the permanent disfiguring effects of such administration. One of the most depressing aspects of the saga is the involvement of organized medicine and the universities in the program. The only evidences of decency in the report are that they never seem to have used veterinary drugs (although they did use agents that had not safety assessment) and they tried to resist the pressure of the coaches to administer the drugs to children below the age of 12 (64). At any rate, more than 2000 athletes were treated each year; male athletes were started at age 16 or 17, and girl swimmers were started at age 14. The doses varied for different sports, weight lifters taking 10 g or more per year whereas women track stars took 1 to 4 grams per year, and the records document the androgen regimens of numerous world-record holders and medal winners at International competitions, including virtually all the GDR gold medal winners in swimming events since the 1976 Olympic games (64). Even in the GDR, however, there was a simultaneous black market because coaches and many athletes did not believe that they were being given high enough doses and wanted more [the athletes

were told officially that they were being given vitamins not steroids] (64). The deleterious impact that this publication has had on enforcement of drug bans in this country will be discussed below.

We do not know of course what went on the other countries behind the iron curtain (suspicious though we may be), but it is known that many of the trainers and sports physicians involved in the GDR program fled Germany to avoid prosecution after the fall of the Berlin wall and are now working for sports federations in other countries, notably in China.

Is Androgen Abuse Harmful? The side-effects vary with the androgen, the dose and duration of administration, and the age and sex of the user. Physiological effects of the hormone are toxic in an inappropriate setting, such as virilizing actions in women and young boys. Side effects that are due to metabolites of the drugs (estrogens for example) occur with most but not all androgens. Other side effects (impairment of hepatic function by 17-alkyl substituted androgens) are the consequence of pharmacological alterations that have no relation to hormonal effects. Finally, some side effects (altered lipoprotein levels) may be dose related and may or may not be mediated by the androgen receptor. Finally, there is wide variability in the incidence of side effects, partly related to age (the younger the individual the more striking the side effects), to the presence of coexisting clinical conditions, to interactions with other drugs, and to the duration and pattern of administration.

It is a given that the virilizing effects of androgens in children and women can be profound and in large part irreversible. Children are particularly susceptible to premature closure of the epiphyses and to both the virilizing and feminizing side effects (65). The virlizing effects in women, including hirsutism, acne, coarsening of the voice, hypertrophy of the clitoris, and male pattern baldness, are also largely irreversible (66,67.) Some German women developed amenorrhea, infertility, and supposedly polycystic ovarian disease, and an increase in female libido was particular problem in the training camps, as a consequence of which all women were simultaneously given oral contraceptives (64). The fact that the side effects in women and children are severe has not prevented their use by these groups (44,66,67).

The question of toxicity in men is somewhat more complicated. Supraphysiological levels of androgens inhibit the secretion of LH and FSH, decrease testicular volume by about 20 percent, and decrease sperm production by 90 percent or more (68-71). When testosterone is raised above the physiological range, body weight increases about 3 percent (in large part due to expansion of the ECF), hemoglobin increases about 1 g/dL, and serum estradiol doubles (69). The stacking regimens used by male athletes can cause complete azoospermia (72), and a hypogonadal state can persist for up to manymonths after the agents are discontinued, apparently the consequence both of prolonged suppression of LH and testicular refractoriness to LH (73,74).

Feminizing side effects are due to the fact that testosterone and other androgens with a Δ4,3-keto configuration can be aromatized to estrogens. In athletes on stacking regimens

plasma estradiol levels can increase as much as 7-fold, levels comparable to those in ovulating women (50). Gynecomastia is very common in men who take androgens (50) and is particularly prominent in children and men with liver disease (75).

All 17α-alkylated steroids have the capacity to cause obstructive liver disease and jaundice (76) and to cause increased levels of several plasma proteins (77). Most abnormalities of liver function regress when the agents are stopped (78), but more serious liver disease may occur, including peliosis hepatitis and hepatoma (79-81). Life-threatening liver damage clearly occurred in men in the GDR (64). Depression of high density lipoprotein cholesterol and elevation of low density lipoprotein cholesterol levels are consistent features of androgen abuse (82-84), and the fact that an increase in atherogenic events is not common suggests either that a lag phase of many years is required for such effects to be observed or that the intermittency of administration protects against the atherogenic effects. It is noteworthy that virtually all reports of serious complications are isolated reports and that no extensive, careful long term follow-up studies have been reported.

In summary, the potential long term toxicity is real, and there is ample reason for the drugs to be banned on medical grounds in men as well as in women and children. To keep things in perspective, however, androgen abuse in adult men is probably not as dangerous as many other risky behaviors.

What Is To Be Done?

Three approaches have been tried to promote ethical behavior in sports—drug testing, education, and what I will refer to as the Greek solution—have been tried:

Drug Testing In view of the fact that other approaches were ineffective, sports organizations and clinical chemists have made an enormous investment in developing sophisticated techniques for detection of drugs of abuse (85-91). To this end, a variety of laboratories around the world have been certified as meeting the standards of the International Olympic Committee. The focus of this program has been almost exclusively on urine testing (neither blood or hair tests are used). With the exception of two central problems—blood doping with autologous blood and the administration of tesotsterone esters—these tests can detect almost all examples of drug abuse on the day of ingestion or shortly thereafter. Because testosterone intermingles with the endogenous hormone, no valid means of detecting its use has been developed, although attempts are still being made (90, 91).

Urine testing—mandatory, carefully monitored, and unannounced as to when it is to be performed—has had at least limited success. As one example, between 1986 and 1989 the IOC-accredited laboratories tested random urine samples from more than 170,000 athletes and identified banned substances in nearly 4000, including androgens in 2362 of the urines (92). The Scandinavian countries have utilized the technique of unannounced, mandatory out-of-competition testing aggressively and effectively. For example, between 1977 and 1995 the Norwegian Confederation of Sport submitted 15,208 urine samples to

IOC laboratories, and they report that as testing frequency increased, the incidence of positive urine tests declined in three high-prevalence sports—power lifting, weight lifting, and athletics (93). The trend does not imply that these sports are free of doping, only that there less doping with impeded androgens than before.

The criticism directed to the United States has been that when athletes test positive in such programs, the sports federations tend to ignore the results and allow the individuals to continue to compete with a warning to clean up their act before in competition testing. My reading between the lines is that this criticism of our sports federations is true and that the probable reason for the unenthusiastic enforcement is that these federations are controlled by (or influenced by) athletes who feel that they have been disenfranchised by the system, particularly by the evidence that androgen administration was almost universal in the GDR but in twenty years only two GDR athletes ever tested positive for androgen use in competition (64). Likewise, they are aware that there is no test for the most widely abused androgen, testosterone and that all urinary androgen tests become negative within a few days of stopping the drug, long before the effects of the drug on muscle dissipate (54). For example consider the number of positive urine tests for androgens at the recent Olympic Games:

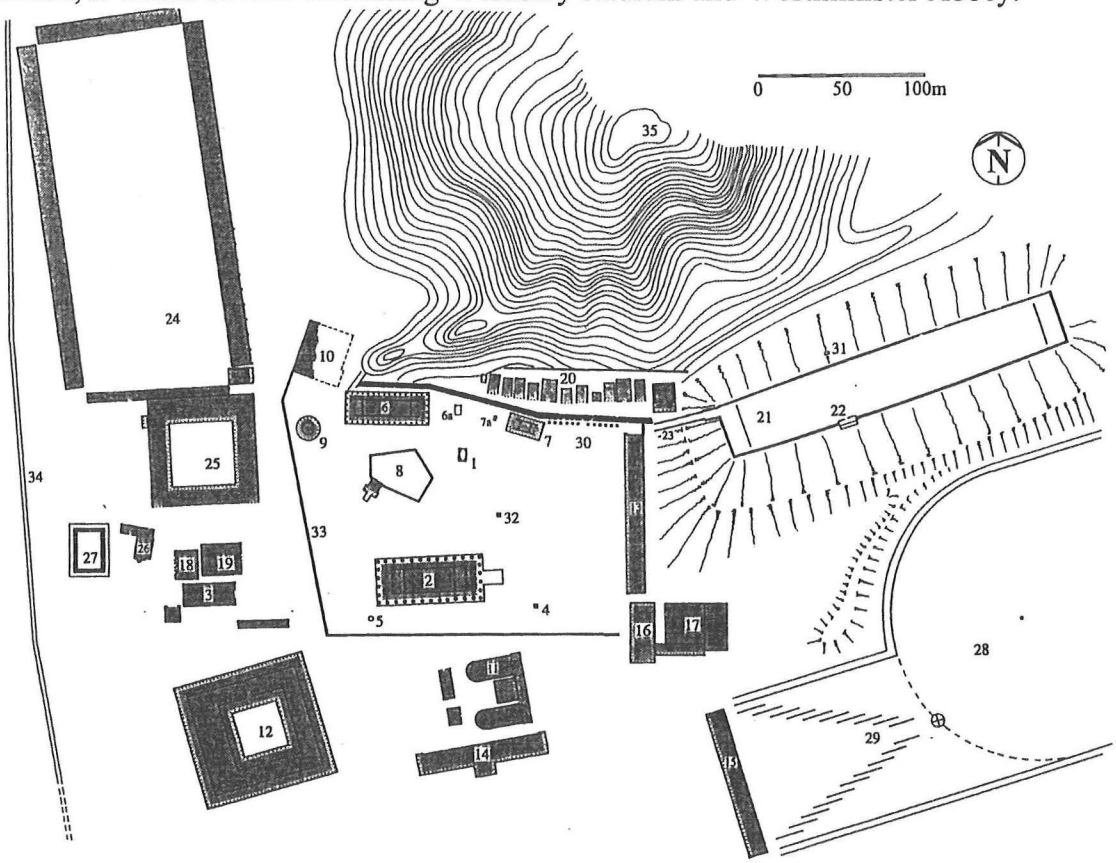
1984	Los Angeles	12 urines positive for androgens
1988	Seoul	1 urine positive for androgen
1992, 1996, 2000		0 urines positive for androgen

This occurred despite the fact that abundant indirect evidence indicates that androgen abuse is more widespread than ever before. For example, every member of the Canadian Olympic Track Team in 1988 testified under oath that they had all been given stanozolol by the team physician and that all of them (except for the one individual who tested positive) had followed instructions and stopped administration a week before the games. Likewise, many GDR champions at the 1992 Barcelona Olympics testified in court proceedings that they were on androgens at the time of the competition (64). It is a widespread feeling that a system is inherently unfair that allows many offenders to obtain the positive benefits of the drugs and escape detection. Consequently, the passive resistance to enforcement of out-of-competition testing made it mandatory for the control to be taken out of the hands of the people who can benefit from taking the drugs and placed in a neutral body.

The limitations of drug testing should not be overstated. Catlin has argued convincingly that some drug use is inhibited by drug testing and that things would be much worse if it did not exist (92). In keeping with this view it is of interest that since the Moscow Olympic Games (the last one in which there was no drug testing) the world's best records have fallen in several women's sports, namely down 7 meters for the javelin throw, 6 meters for the discus, and 2 meters for the shot put (64). The winner in the javelin throw in Atlanta would have been number six in Moscow (64). Consequently, the effort to improve drug testing will continue.

Education After the Seoul Olympics the Canadian Government set up an antidoping agency (the Canacian Centre for Ethics in Sports) that has been at work for more than a decade. They have tried a variety of approaches with elite athletes, all unsuccessful, and have decided to place the major emphasis on an educational campaign directed to children and teenagers, modeled after antismoking programs for the same age group, in the hopes that such an approach can make the use of performance enhancing drugs socially unacceptable. In the United States the National Institute on Drug Abuse launched a similar program addressed to adolescents in 1994, including a website (www.steroidabuse.org) and extensive educational materials. The educational approach may be no more successful than drug testing but it can hardly be less so.

Greek Solution Perhaps the best solution for dealing with cheating in competitive sports was that practiced in the ancient Olympic games. Every fourth year for a thousand years—776 BC to 395 AD--the Olympic Games attracted citizens from all over the Greek world, including colonies as far away as Spain and Africa. The Games were held in honor of Zeus, the supreme God of Greek mythology, and a visit to Olympia in the western Peloponese was a pilgrimage to his most sacred place. As Swadling has phrased it, the combination of a sports complex and a center for religious devotion has no modern parallel; it would be like combining Wembley stadium and Westminister Abbey.



PLAN OF OLYMPIA C.100

1 Great Altar of Zeus
2 Temple of Zeus
3 Pheidias' workshop
4 Statue ofVictory by Paionios
5 Sacred olive tree
6 Temple of Hera
6a Altar of Hera
7 Temple of Rhea
7a Altar of Rhea
8 Pelopion
9 Philippeion
10 Prytaneion
11 Bouleuterion
12 Leonidaion
13 Echo Colonnade
14 Southern Colonnade
15 Colonnade of Agnaptos
16 South-Eastern Colonnade
17 'Greek building'
18 Heroon
19 'Theokoleon'
20 Treasuries
21 Stadium
22 Judges' stand
23 Entrance tunnel to stadium
24 Gymnasium
25 Palaistra
26 Bathing facilities
27 Swimming pool
28 Hippodrome
29 Starting gate for horse-races
30 Zanes (statues of Zeus)
31 Altar of Demeter Chamyne
32 Pillar of Oinomaos
33 Altis wall
34 Retaining wall of river Kladeos
35 Hill of Kronos

The archeological site, one of the largest and arguably the most important Greek site of the classical age outside of the Athenian acropolis, has been the subject of intense study and reconstruction since the mid 19th century. The site contains three principal areas: the *training area* consisting of a gymnasium and palaestra, the *Altis* or sacred area containing the Temples of Zeus and Hera, where the competitors prayed and made sacrifices prior to competing, and the *stadium* where the athletic competitions were held and the *hippodrome* for esquedrian events. Just before the beginning of the competitions the athletes performed their religious rites and then moved either into the hippodrome or through an arch that still exists into the stadium. In doing so, each competitor had to pass the Zanes, a row of small statues of Zeus along the terrace wall, each erected to commemorate an episode of cheating. When cheating was uncovered (the use performance-enhancing drugs [bread soaked in opium] was apparently not considered cheating, instead the major crime was bribery), the home city was fined, and the fine was used to erect a statue to commemorate the episode, on the plinth of which was described the culprit, the event and date on which the cheating took place, the home city, and the name of the father—a permanent shame to the individual, his family, and his city. According to Pausanius, there were sixteen such statues, six of which were erected from fines imposed on the city of Athens; twelve plinths still exist today. If there were in fact only 16 examples in a thousand years, then it means that this system was either very successful (or very unsuccessful). Today there is no permanent site for the games, but perhaps a modern version could be devised. Shame seems to be out of fashion in modern life, but ridicule might be appropriate for a cheaters website or a hall of dishonor at the homes of the International Olympic committee and the various national committees. Thinking along these lines could hardly be less successful than what has been tried to date.

CONCLUSION

The desire to excel at sports is so intense that it drives athletes (and governments) to extreme ends to win, including the use of drugs with potential for harm. This practice appears to be increasing in frequency and has poisoned the atmosphere of international competition in sports. It is not intuitively obvious (to me) what should be done to contain this epidemic, but it is unlikely that drug testing will ever provide more than a partial answer.

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