

Doping Control for the Team Physician

A Review of Drug Testing Procedures in Sport

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Drug testing is now ubiquitous in sport, and it often falls to the team physician to perform a variety of roles including interpreting test results, designing drug-testing programs, acting as medical review officer, and providing therapeutic use exemptions, education, and counseling. Proper understanding of current testing methods for drugs such as anabolic-androgenic steroids, erythropoietin, and growth hormone is essential if the team physician is going to assume these positions. This article outlines the basics of athletic drug testing from the collection process through the interpretation of results to assist the team physician in this field.

Keywords: drug testing; anabolic-androgenic steroids; erythropoietin; human growth hormone; drug education

As compared with other aspects of sports medicine, the issue of doping control is a unique area for the team physician. The physician is usually the leader of the medical team and has ultimate authority on medical decisions. This is a natural extension of the physician-patient relationship in which the physician has a fiduciary relationship to protect the health of the athlete who is considered first and foremost a patient. These and other factors complicate the relationship and have led to the physician becoming one part of the doping-control process rather than the leader and final arbiter. Organizations such as the World Anti-doping Agency (WADA) have been created to develop standards and a consistent, worldwide doping-control program. The 2006 WADA list of prohibited substances can be found in Table 1.

Within the sports medicine environment are issues relating to drug use that affect both the athlete and team physician and that may strain their traditional relationship. For example, a positive drug-test result may cause significant conflict because of an athlete's professed innocence or the physician may have knowledge gained in the patient-doctor relationship that cannot be disclosed. Alternatively, a physician may be part of a drug-testing program and responsible for determining a positive finding that results in punishment for the athlete whom he or she is caring for. There may also be the situation in which a

physician serves a sports organization or team whose interests conflict with the athlete's health needs.

The doctor-patient relationship is a significant issue in doping control, and many physicians providing athletes with banned substances have used this as a justification for their actions. Hoberman¹⁸ wrote that some physicians maintain the doctor-patient relationship trumps any doping-control regulations. This view has largely been supplanted by the antidoping organizations that now regulate international sports. Although there have been physicians with less-than-altruistic motives, some doctors prescribed banned substances on the basis of a harm-reduction model, for example, prescribing methadone to a heroin addict to prevent the attendant risks associated with illegal and parenteral drug use. Unfortunately, the dose-dependent performance effects of drugs like anabolic-androgenic steroids (AAS) often lead athletes to ignore physician-prescribed dose limitations and augment legitimate prescriptions.

The often complicated relationship between physicians and drugs in sport has a long historical legacy. As the traditional dispenser of medicine, physicians have been sought out by athletes to provide performance aids since the ancient Greek Olympics. This trend continues, as evidenced by the 2005 National Collegiate Athletic Association Survey of Use and Abuse Habits of Collegiate Athletes. When anabolic steroid users were asked to identify their sources of the drugs, 13% named a physician, which was a leading response.²¹

Although team physicians are usually not the final authority with respect to drug testing, they play a central role in the use and abuse of drugs by athletes. Physicians are often asked to provide education, act as medical directors or medical review officers for drug testing, and provide therapeutic use exemptions (TUEs). It is therefore imperative that physicians who serve as team physicians be familiar not only with performance-enhancing drugs used by athletes but also with

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TABLE 1
World Anti-doping Agency 2006 Prohibited List

Prohibited substances	
S1.	Anabolic agents
	1. Anabolic androgenic steroids
	a. Exogenous
	b. Endogenous
	2. Other anabolic agents (eg, clenbuterol, zeranol, zilpaterol)
S2.	Hormones and related substances
	1. Erythropoietin
	2. Growth hormone, insulin-like growth factor
	3. Gonadotropins
	4. Insulin
	5. Corticotrophins
S3.	Beta-2 agonists
S4.	Agents with anti-estrogenic activity
	1. Aromatase inhibitors
	2. Estrogen receptor modulators
	3. Other anti-estrogenic substances
S5.	Diuretics and other masking agents
S6.	Stimulants
S7.	Narcotics
S8.	Cannabinoids
S9.	Glucocorticosteroids
Prohibited methods	
M1.	Enhancement of oxygen transfer
M2.	Chemical and physical manipulation
M3.	Gene doping
Substances prohibited in particular sports	
P1.	Alcohol
P2.	Beta-blockers

the procedures used to determine a positive test result. The high-profile nature of sports medicine is a dual-edged sword, as mistakes are often magnified. At the 2000 Summer Olympics, a Romanian team physician inadvertently provided a gymnast with pseudoephedrine, which was banned at that time, leading to her disqualification and medal loss, as well as his own 4-year suspension. Although this article provides a current overview for the team physician, the rapidly changing landscape of drug use in sports necessitates constant attention to emerging trends and regulations.

This article will focus on the types of drug testing that are performed with respect to performance-enhancing drugs. The actual effects of these drugs are beyond the scope of this article, and there has been a recent review in this journal.²⁵ In many organizations, it often falls to the team physician to interpret positive and negative drug-testing results, and a basic knowledge of these tests is essential. Too often, an institution or sports organization will blindly rely on drug-testing results and ignore clinical judgment. It is the physician's obligation to place drug testing in the proper context of one tool in the antidoping armamentarium.

Collection and Chain-of-Custody Issues

Physicians are often asked to interpret drug tests because of their familiarity with ordering and understanding medical

studies. However, drug testing is much different from basic biomedical testing, and it is imperative the team physician understand the distinction. For example, athletic drug testing begins with witnessed urine collection according to a rigorous set of standards that must be adhered to in order to have a valid sample. The collection process is the first step in a strict chain of custody. In sports drug testing, chain of custody usually describes any written procedures to ensure that the collection, transportation, and laboratory analysis of urine, blood, or other specimens remain secure from outside tampering, review, or disclosure. Chain of custody usually includes 3 facets of the testing process: collection, transportation, and laboratory analysis.²⁷ Any deviation from the chain of custody invalidates the test.

The collection of urine specimens in sports drug testing is a sequential process with many steps. Such steps include but are not limited to the following: athlete selection (ie, random, announced, unannounced), identification of the athlete to be tested, selection of a collection container by the athlete, the voiding process under the direct observation of a same-sex validator, specimen integrity checks (eg, specific gravity, pH), specimen numbering and packaging by the athlete or by the collector under the athlete's watch, and the certification by all parties that the published collection process was followed. Once completed, the typical protocol is for the athlete's sample to be divided into "A" and "B" bottles that are both securely sealed. These steps are essential because when athletes challenge the validity of positive drug-test results, the integrity of the collection process often is called into question.²⁸ The increased legal scrutiny of the process has led to the formation of independent companies that serve as "third-party administrators" for the drug-testing process.

Once the sample has been sealed, it is securely transported to an accredited laboratory. Although there are a variety of commercial laboratories in the United States that perform workplace drug testing and are certified by organizations such as Substance Abuse and Mental Health Services Administration, WADA has a rigorous certification process for those laboratories that are qualified to perform Olympic-caliber testing. The WADA certification signifies not only the quality of the laboratory but expertise in testing for the specific drugs on the WADA prohibited list. As of this writing, there are 32 WADA-certified laboratories throughout the world and 2 in North America (Montreal and Los Angeles).

Once received by the laboratory, the samples are immediately examined to ensure there has been no break in the chain of custody. An internal chain of custody is generated to allow tracking of the sample throughout the analytical process and to account for each individual who has access to that particular sample. Initially, only the "A" bottle is unsealed and undergoes screening analysis. If the screening result is negative, no further testing takes place, and eventually both the "A" and "B" bottles are discarded. However, in the event the "A" screening result is positive, a confirmation test is performed on a new aliquot from the "A" bottle. Only if the "A" confirmation is positive are the results reported to the sports organization. At this point, the athlete is generally entitled to have the "B" sample analyzed and is allowed to either witness the analysis or have a representative present.

TABLE 2
Summary of Testing and Period of Detectability^a

Banned Drugs	Example of Screening Technology	Example of Confirmation Technology	Period of Detectability
Stimulants	GC-MS	GC-MS	A few hours to a few days
Anabolic steroids	GC-MS; LC-MS-MS ^b	GC-MS	Days to months ^c
Diuretics	LC-MS-MS	GC-MS	A few hours to a few days
Marijuana	GC-MS and immunoassay	GC-MS	Some weeks
EPO	IEF	IEF	A few days

^aGC, gas chromatography; MS, mass spectrometry; LC, liquid chromatography; EPO, erythropoietin; IEF, isoelectric focusing.

^bLiquid chromatography–mass spectrometry–mass spectrometry is a process in which the separation phase occurs in the liquid phase rather than in the gas phase with GC-MS.

^cAnabolic steroids can be detected for as short as only a few days or as long as many months after the user stops taking them, depending on type used (eg, short-acting pill or long-acting oily injection), and some steroids are easier to detect than others because of chemical differences.

The “B” bottle is then unsealed for the first time and analyzed and confirmed. If the “B” does not match the “A” result, it is considered a negative test result. In summary, by the time a positive result is reported, there have been at least 2 and usually 3 separate analyses performed on the athlete’s sample that all yield the same result.

SPECIFIC ANALYTICAL METHODS

The next several sections will discuss various specific methods that the team physician should be familiar with to interpret drug-test results. Although not inclusive of all testing, these represent some of the more common performance-enhancing drugs that offer challenges in interpretation. A summary of some substances and tests is listed in Table 2.

Anabolic-Androgenic Steroids

Anabolic-androgenic steroids represent an area of great concern because of their ability to enhance strength and influence the integrity of sports. There are 2 types of AAS that are identified by drug testing: exogenous (xenobiotic) or endogenous compounds. Some of the more common AAS are listed in Table 3. The relative “popularity” of these types of AAS depends to a large degree on the detectability of various drugs, and testing for AAS has been an integral part of doping control since the 1970s. The introduction of gas chromatography–mass spectrometry (GC-MS) to doping control in the 1980s heralded a new era, and in the past 2 years, several designer AAS have been identified, including tetrahydrogestrinone, norbolethone, and madol.^{4,8,24}

The GC-MS testing involves separating the components of a mixture based on chromatographic retention time and fragmenting each component to its characteristic ions. Identification is achieved by matching the relative retention times and mass spectra of the parent drug or metabolites with those of known reference standards. The finding of metabolites confirms that the individual had in fact ingested the AAS in question.⁶

TABLE 3
List of Common Anabolic Steroids

Generic Name	Trade Name
Testosterone	Depo-testosterone
Nandrolone	Deca-durabolin
Methandrostenolone	Dianabol
Oxandrolone	Oxandrin/Anavar
Oxymetholone	Anadrol
Stanozolol	Winstrol
Trenbolone ^a	Finaplix
Boldenone ^a	Equipoise

^aVeterinary products.

The assay procedure involves a series of chemical steps designed to improve the fragmentation process of the target drug and make it much more amenable to detection in the GC-MS. A GC-MS can be operated in either the full-scan or the more sensitive ion-monitoring mode. Typically, steroid-screening tests are conducted in the sensitive ion-monitoring mode. If a banned drug is detected, a confirmation test must be employed for definitive identification. The more specific full-scan mode is used for confirmation when the concentration of AAS is high.¹² The introduction of more sensitive instruments (eg, high-resolution MS) in doping control has extended the period of detectability of exogenous AAS. For example, methandienone may be detectable for so much longer that laboratories now screen for a different, late-forming, long-lasting metabolite.

The AAS nandrolone, or 19-nortestosterone, deserves special mention as it is one of the most commonly detected exogenous AAS, and there is a great deal of confusion regarding positive test results. Some of the reasons for this are the long period of detection after injection of nandrolone decanoate and ubiquity of 19-norandrostenedione. The first clarification is that a “nandrolone” positive does not indicate that the AAS nandrolone was found in the urine. In actuality, the laboratory measures 2 metabolites of nandrolone, 19-norandrosterone (19NA) and 19-noretiocholanolone (19NE),

with the former more commonly reported. Further confusing the situation is that 19NA and 19NE can result from the use of nandrolone, 19-norandrostenedione, or 19-norandrostenediol.¹⁵ Until the passage of the 2004 Anabolic Steroid Control Act, these latter 2 were available as dietary supplements, creating more misinterpretation. It was also discovered that microgram amounts of 19-norandrostenedione, which could occur from contamination, can result in a positive test result.⁷ Furthermore, there is no practical method of determining which of the 3 substances resulted in the positive test result. In general, this is a moot point in that all 3 compounds are banned by most sports organizations. In addition, most sports authorities have adopted "strict liability" for drug-testing offenses, and contamination has not been held as a viable defense.

The second area of clarification is that whereas the mere presence in the urine of other exogenous AAS is reported as a positive, nandrolone (or more properly 19NA) is reported with a specific concentration level. This is because small amounts of 19NA can occur without ingesting a prohibited substance, and because of that, WADA has set the cutoff level for 19NA as 2 ng/mL. Pregnant women will excrete small amounts of 19NA, and consumption of oral contraceptives containing norethisterone may result in the excretion of small amounts of 19NA. The latter case can be resolved by the finding of specific norethisterone metabolites.¹⁷ It has also been found that some males may naturally produce miniscule amounts of 19NA in the urine and that there is a great deal of interindividual variability with respect to nandrolone excretion.²

There has also been controversy regarding nandrolone-positive test results due to dietary interference or exercise effects. Athletes have claimed that consuming large quantities of uncastrated boar organs resulted in a positive test result for nandrolone metabolites.²⁰ Although highly improbable, a positive test result could technically result from consuming more than a half-pound of uncastrated boar testicles, liver, and kidney within 24 hours of a test. Intense exercise was also mentioned as a potential cause of elevated 19NA levels, but studies have refuted this claim.^{23,26}

Last, the use of injectable nandrolone decanoate has been detected by urine testing for many months and in some cases more than a year. This creates a quandary for sports authorities to determine if a repeat positive test result represents continued use. Many sports organizations require a clean "exit" urine test before allowing an athlete to return from suspension, whereas others do not make any exception for multiple positives from a single use. The philosophy in this latter case is that parenteral use is a more serious offense and that the athlete receives a continued advantage with a long-acting AAS.

As testing for xenobiotic AAS improved, athletes predictably used endogenous compounds (eg, testosterone) as an ergogenic aid. Testosterone is problematic because pharmaceutical testosterone and endogenous testosterone have identical patterns on MS. Since 1983, the accepted approach has been to monitor the testosterone/epitestosterone (T/E) ratio that normally exists in approximately a 1:1 ratio.⁹ The use of testosterone, or compounds that increase testosterone (ie, DHEA, androstenedione, androstenediol, etc), will raise

urinary testosterone proportionally much more than epitestosterone. A level greater than 6:1 was considered an indication of testosterone use. Athletes have attempted to subvert the test by taking epitestosterone (a biologically inactive compound) in conjunction with testosterone to maintain a normal T/E. To prevent this, epitestosterone is quantified, and concentrations above 200 ng/mL result in a positive test result. Because of these factors, WADA, and thus all international federations that are signatories to WADA, lowered the threshold in 2005 and decreed that a T/E ratio of greater than 4 requires further investigation.

An elevated T/E ratio is a common reason for the team physician to be consulted by the athlete or sports organization. The main limitation of the T/E ratio is that there are a small percentage of individuals who are naturally in the 4 to 10:1 range, despite not using testosterone or related compounds. Several options exist in these individuals to determine whether they are misusing testosterone or have a "naturally occurring" elevated T/E ratio. The most common method is to perform serial, unannounced drug tests and compare the results. The T/E ratio is relatively stable, and a marked drop in T/E would be suggestive of previous use; WADA recommends 3 unannounced tests in a 3-month period.³⁰

Multiple T/E-ratio testing has the disadvantage of requiring a great deal of time and expense and still can be subverted by an athlete carefully monitoring his or her T/E. Media coverage from the US BALCO affair revealed that athletes were given a cream containing both testosterone and epitestosterone to maintain their T/E ratios. An alternative to serial testing is the ketoconazole challenge in which the drug ketoconazole is orally administered and the T/E measured. Normal males will react to ketoconazole by suppressing testosterone and a reduced T/E, whereas T/E increases in the face of exogenous testosterone administration. In fact, this test is rarely employed. The most reasonable solution is likely to be carbon isotope ratio testing (also called isotope ratio MS [IRMS]), which can differentiate exogenous testosterone and/or epitestosterone from that which is naturally occurring.¹²

Gas chromatography-combustion-IRMS is a new tool that WADA accepts as a method of determining whether an elevated T/E ratio is the result of exogenous testosterone use. This test can detect small differences in the isotopic composition of organic compounds relative to an international, conventional reference standard. The IRMS is based on the finding that 98.9% of the carbon atoms in nature are ¹²C, with 1.1% being ¹³C, an isotope of carbon that contains an additional neutron. The ratio of ¹³C/¹²C can be measured with high accuracy and precision by an isotope ratio mass spectrometer. Accordingly, very small differences in the abundance of ¹³C can be detected to allow differentiation of carbon sources. The IRMS values for steroids are expressed as delta values: $\delta^{13}\text{C}\%$. The more negative a delta value, the less ¹³C the compound contains.

The basis for IRMS is that plants fix atmospheric CO₂ at varying rates, and most plants fall into 1 of 2 main photosynthetic processes, C3 or C4, that each yield different amounts of ¹³C content. The C3 plants, such as soybeans, are considered isotopically "light" as they fix relatively less ¹³C. On the other hand, C4 (eg, corn) plants incorporate

more ^{13}C and are thus “heavy” with respect to their carbon. Most humans eat both plants and animals containing various amounts of ^{13}C , and studies have determined ethnic differences in the IRMS of different populations, depending on their respective diets. The IRMS has also been shown to be sensitive to changes in diet and the total amount of ^{13}C consumed. As applied to the detection of anabolic steroids, IRMS has the ability to distinguish exogenous from endogenous testosterone. Pharmaceutical testosterone is manufactured from stigmaterol (a soy compound) that contains relatively less ^{13}C content as compared with endogenously produced testosterone, thus yielding significantly different results on IRMS analysis.

The IRMS testing can determine much more than the amount of ^{13}C in urinary testosterone and can provide more definitive information as to the source. After pharmaceutical testosterone administration, the delta values of urinary testosterone metabolites, such as androsterone and etiocholanolone, will drop. In contrast, the delta values of testosterone precursors, or endogenous steroids not involved in testosterone metabolism, will not change. These compounds can be used as endogenous references. A significant difference in the delta value between testosterone or its metabolites and an endogenous reference compound indicates an exogenous source of testosterone or of any steroid in its metabolism. Looking for such gaps is a superior approach because the delta value of testosterone alone in a nonuser might be affected by factors such as diet and is difficult to interpret. Comparing metabolites to precursors provides strong indication of the use of testosterone or its precursors such as androstenedione, androstenediol, or possibly DHEA. Mostly the test is done to obtain additional information to consider whether an elevated T/E is consistent with the misuse of male hormones.¹⁶ The IRMS has also been used to resolve cases of low levels of 19NA and 19NE in the setting of potentially “unstable” urine samples.¹

Testing for Erythropoietin and Darbepoetin

The synthesis of a recombinant human erythropoietin (r-HuEPO) in 1987 dramatically changed the landscape of endurance sports events. Although it had been well known for many years that increasing the red cell mass would improve VO_2 max, before 1987, rapid increases in hemoglobin could only be accomplished through the inconvenient, complicated, and potentially dangerous process of packed red blood cell transfusions. The advent of r-HuEPO meant that a simple subcutaneous injection could increase the hematocrit to the desired level. Even more advantageous, r-HuEPO and its long-acting cousin darbepoetin (introduced in 2001) are nearly identical to naturally produced EPO, making detection by conventional means impossible. The only difference is the presence of additional sugar chains on the synthetic compounds. Although these substances were banned by the International Olympic Committee in 1990, the lack of an effective test led to reports of rampant use in sports such as long-distance running and cycling. Despite a previous report in the literature,²⁵ neither GC-MS nor high-performance liquid chromatography can be used to detect r-HuEPO.

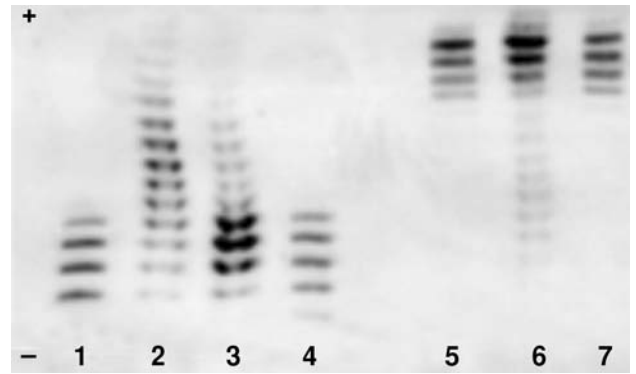


Figure 1. Electropherogram of r-HuEPO (lanes 1 and 4) and darbepoetin alpha (lanes 5 and 7) standards and extracts of urine obtained from healthy controls (lane 2) and individuals treated with r-HuEPO (lane 3) and darbepoetin alpha (lane 6). r-HuEPO, recombinant human erythropoietin. Reprinted with permission from Catlin DH, Breidbach A, Elliott S, Glaspy J. Comparison of the isoelectric focusing patterns of darbepoetin alpha, recombinant human EPO, and endogenous EPO from human urine. *Clin Chem*. 2002;48:2057-2059.

The detection of r-HuEPO was attempted through both blood and urine testing. The blood tests rely on an index of various markers, such as hematocrit, reticulocytes, and iron parameters, that are known to change after the administration of nonphysiologic r-HuEPO.²² This test is considered “indirect” or “pharmacodynamic” because it measures the effect of the drug rather than the actual drug or metabolite, as in GC-MS testing for AAS. The urine test takes advantage of the extra sugar molecules on r-HuEPO and darbepoetin. This glycosylation allows for separation of exogenous and endogenous EPO in a pH gradient electrical field and detection with a very sensitive and selective method. This results in the so-called isoform patterns of EPO in urine,¹⁹ and the isoform pattern of r-HuEPO is distinctively different from that of natural EPO. The isoelectric focusing urine test also yields a pattern for darbepoetin that is distinct from both EPO and r-HuEPO.³

The urine method provides a direct test for r-HuEPO and has been upheld in court many times since 3 cross-country skiers tested positive for darbepoetin at the 2002 Salt Lake City Olympics. Figure 1 demonstrates the differences between natural EPO, r-HuEPO, and darbepoetin as seen on an electropherogram.⁵ Although it is unlikely that a team physician would be asked to interpret an electropherogram, it is important to understand the process when confronted with a positive finding for these substances.

Testing for Human Growth Hormone

The validation of a test for r-HuEPO left growth hormone as the major challenge for drug detection in the 21st century. Similar to EPO, the synthesis of a recombinant form of human growth hormone (rhGH) in the late 1980s freed athletes and patients alike from dependence on small supplies of cadaveric hGH and its attendant infectious risks.

Since its introduction, multiple anecdotal reports have appeared: Ben Johnson's 1988 admission of combining rhGH with anabolic steroids, the discovery of large amounts of rhGH in a Tour de France support vehicle in 1998, and the confiscation of rhGH from the baggage of Chinese swimmers before the 2000 Sydney Olympics.¹⁴

Naturally occurring hGH is a polypeptide hormone of 191 amino acids that is produced in the anterior pituitary at a rate of 0.4 to 1.0 mg/d in healthy adult men. Natural hGH is secreted in the form of multiple isoforms, with the predominant one being a 22-kD isoform and about 10% being the 20-kD form. This is in contrast to rhGH, which contains only the 22-kD isoform. Parenteral administration of rhGH peaks in 1 to 3 hours and is imperceptible at 24 hours. Administration of rhGH stimulates the production of various markers, the most prominent being insulin-like growth factor (IGF-1) or somatomedin-C and others such as procollagen type III and osteocalcin. Although there is some debate about whether substances such as hepatic-produced IGF-1 are markers or mediators, hGH exerts most of its effects through receptors at target cells.

Because of the lack of glycosylation, the isoelectric focusing method developed for r-HuEPO cannot be directly applied to rhGH. Although no definitive test yet exists for the detection of rhGH, there has been some progress of late. One method measures the amount of the 20-kD isomer in the serum, which is present at a level of 10% in normal samples but is suppressed when rhGH is given. This method has shown promise of detecting rhGH within 24 hours of the last dose; however, it requires a blood test and cannot detect cadaveric hGH. Another method relies on pharmacodynamics and measures evidence of supraphysiologic doses of hGH. Recent study has revealed that of the many markers of hGH use, IGF-1 and procollagen type III can consistently discriminate rhGH users from nonusers.³² It remains to be seen whether this approach to drug testing will survive forensic challenges to a system that has traditionally relied on a "fingerprint" identification of the banned substance. Although some testing for rhGH was performed at the 2004 Summer Olympics, the lack of an easily performed test that can withstand a forensic challenge is likely to make hGH an ongoing challenge to doping-control efforts.¹⁴

Interpretation of Drug-Testing Results

There are 2 types of drug-testing results that the physician encounters: (1) the presence of substances for which any amount represents a positive test result and (2) tests that have cutoffs or thresholds of reporting. The former are relatively easy to interpret in that the test result is either positive or negative and levels are not relevant. In the latter category, we have discussed examples such as nandrolone (19NA) and testosterone and epitestosterone in conjunction with the T/E ratio. Other substances are not reported as a positive test result unless they exceed certain levels. Examples of this include the stimulants cathine, caffeine, and ephedrine. In addition, many sports organizations set a threshold for tetrahydrocannabinol (THC), the active ingredient in the recreational drug marijuana. A level of 15 ng/mL is high enough to distinguish between passive inhalation of

TABLE 4
Substances With Threshold Reporting Levels

Substance	Reporting Threshold
Caffeine	15 µg/mL ^a
Cathine	5 µg/mL
Ephedrine	1.5-10 µg/mL ^b
Epitestosterone	200 ng/mL
Methylephedrine	10 µg/mL
Morphine	1 µg/mL
19-norandrosterone	2 ng/mL, males
Salbutamol	1 µg/mL
Tetrahydrocannabinol	15 ng/mL
Testosterone/epitestosterone ratio	>4:1; >6:1 ^c

^aCaffeine is monitored by the World Anti-doping Agency (WADA) but not subject to sanctions.

^bThe WADA and National Collegiate Athletic Association (NCAA) threshold is 10 µg/mL; the National Football League (NFL) threshold is 1.5 µg/mL.

^cThe WADA and NFL threshold is 4:1; the NCAA threshold is 6:1.

marijuana smoke and actual use. Because of its half-life of 2 weeks and popularity, a positive test result for THC is frequently encountered in the athletic population. When evaluating an athlete with a positive drug-test result for THC, it is incumbent on the professional to thoroughly review the athlete's drug history and not merely focus on marijuana use. In the author's experience, athletes with a positive test result for THC are more likely to have a problem with drugs other than THC, such as alcohol or cocaine.¹³ Substances with reporting thresholds are summarized in Table 4.

In addition to interpreting levels and positive results, it is important to understand what a positive test result can and cannot reveal. A positive test result for a banned drug only demonstrates that the substance or metabolite was in the athlete's urine at the time of the collection. It cannot determine with any certainty the brand or formulation, route of entry (oral or injectable), how much was taken, or when it was taken. As a medical review officer, a physician is often asked by the sports organization for answers to these questions, and it is imperative to understand the limitations of a positive test result.

Finally, it is also essential to be able to correctly interpret negative results. Although modern Olympic-style drug testing is extremely sensitive, it has restrictions, as do all biomedical tests. There are several potential explanations for a negative drug-testing result, the most common one being that the drug was never used. However, there are also other potential reasons. The athlete may have used a particular drug in the past, and it has now been eliminated from the body. In the case of many performance-enhancing drugs, the effective period far outlasts the detection time (see Table 2). For example, serial injections of r-HuEPO will provide an elevated hematocrit for several weeks yet can only be detected for a few days after its cessation. Or a drug had been taken in the past but is below the limits of detection. A negative test result may also occur when an athlete is using a drug, such as a designer drug, that the laboratory cannot detect. Finally, athletes have also managed to invent clever

TABLE 5
World Anti-doping Agency International Standard for Therapeutic Use Exemption (TUE) Criteria^a

1. The athlete should submit an application for a TUE no less than 21 days before participating in an event.
2. The athlete would experience a significant impairment to health if the prohibited substance or prohibited method were to be withheld in the course of treating an acute or chronic medical condition.
3. The therapeutic use of the prohibited substance or prohibited method would produce no additional enhancement of performance other than that which might be anticipated by a return of normal health after the treatment of a legitimate medical condition. The use of any prohibited substance or prohibited method to increase "low-normal" levels of any endogenous hormone is not considered an acceptable therapeutic intervention.
4. There is no reasonable therapeutic alternative to the use of the otherwise prohibited substance or prohibited method.
5. The necessity for the use of the otherwise prohibited substance or prohibited method cannot be a consequence, wholly or in part, of prior nontherapeutic use of any substance from the prohibited list.

^aSee the World Anti-doping Agency International Standard for Therapeutic Use Exemptions.²⁹

methods of urine substitution. This emphasizes the need for professional sample collectors, rigorous vigilance, and strict adherence to written protocols.

Therapeutic Use Exemption

Therapeutic use exemptions recognize that there are some drugs that, although prohibited by sport, have legitimate medical indications. Although this appears obvious on the surface, its application is complex. For example, the use of insulin in a type I diabetic would not be debatable. There are well-established criteria for both the diagnosis and the treatment with easily measured parameters. For other situations, such as the use of stimulants in the treatment of attention deficit hyperactivity disorder (ADHD), there is considerable controversy regarding what constitutes the diagnosis, the necessity of treatment, and the types of medications.

To balance medical necessity with providing an unfair advantage, the TUE process has been developed; WADA has adopted an international standard for TUE, and the 5 basic criteria are listed in Table 5.²⁹ It falls to the antidoping agency of each country to recruit qualified physicians to serve on a TUE committee and review individual cases.

The first condition of the TUE is that it must be done prospectively. The athlete and his or her health care provider must work in concert before an event and secure approval; WADA does grant contingencies for emergency treatment of an acute condition or exceptional circumstances, but the majority of TUEs are reviewed and granted in advance. This is in contrast to other organizations, such as the National Collegiate Athletic Administration, that only consider retroactive TUEs. The second tenet ensures that the medication in question is necessary. As mentioned, this can sometimes be ambiguous, and the TUE committee must rely on the testimony of the treating physician to fulfill this requirement.

The third requirement is to ensure that the athlete does not receive any additional ergogenic benefit other than the return to normal health. In some conditions, for example, an asthmatic using a beta-2 agonist, pulmonary function tests can clearly prove this point. However, other diseases do not lend themselves to a quantitative measure and are more subjective. Because of this, WADA specifically states

that a TUE cannot be granted for "low-normal" levels of endogenous hormones. Given the wide range and individual variability of hormones such as testosterone and growth hormone, this is a necessary caveat.

The fourth principle is that there must be no reasonable therapeutic alternative. Although this is sound in theory with diseases such as diabetes in which insulin is the standard treatment, it becomes more problematic in deciding how far an athlete should go to satisfy this condition. For example, in the treatment of ADHD, atomoxetine is approved for this condition and is not prohibited. Is it reasonable to require that every athlete with ADHD have a therapeutic trial of atomoxetine before being granted a TUE for methylphenidate? It seems onerous and bordering on medical malpractice to take a patient who is well controlled on a medication and substitute another to satisfy a committee. Clearly, this requires medical judgment because if the athlete truly satisfied the second criterion, then it would be contraindicated to apply this requirement.

The final requirement in Table 5 is that the TUE cannot be a consequence to any degree of prior nontherapeutic use of a prohibited substance. This is an important restriction for it also closes a potential gambit to circumvent doping control. For example, after the extended use of AAS (particularly long-acting compounds), the pituitary-gonadal axis will be impaired, often for several months. An athlete could potentially apply for a TUE to use testosterone on the basis of subnormal testosterone levels. This TUE criterion makes it clear that an athlete could not receive a benefit after such use.

The WADA criteria may not be appropriate for every sports organization. It is not an exact science, but it does provide a framework for distinguishing therapeutic from ergogenic drug use. It offers a method of ensuring that all athletes adhere to similar principles with respect to using prohibited substances for legitimate therapeutic indications. Physicians play a key role in reporting accurate information in the TUE application and applying sound medical judgment to their evaluations.

Designing a Drug-Testing/Drug-Education Program

Institutions and organizations often consult team physicians with respect to setting up their own programs. Drug

testing is often a knee-jerk response to reports of drug use by athletes or a positive test result by a supervising agency. In any event, the most important first step is to determine the purpose of the program, as this will shape subsequent decisions. Drug testing is a complicated process, and a poorly designed program is usually worse than none at all. There should be adequate resources available for the collection and testing aspects of the program. The use of third-party administrators to collect the samples is preferred over the use of existing institutional personnel, such as certified athletic trainers. Although it is economically tempting to use these personnel, it creates inherent conflicts among the staff and athletes that can ultimately doom a program. My recommendation would be to use third-party administrators and minimize the involvement of institutional employees. Finally, the highest quality laboratory should be employed, especially if AAS are being tested.

Institutional drug-testing programs also tend to be more successful if as many "stakeholders" support it as possible. This would include administrators, coaches, athletes, certified athletic trainers, and physicians. Interestingly, most studies of athletes reveal that athletes are in favor of drug-testing programs.²¹ In addition to these personnel, it is imperative that legal counsel be involved early in the planning stages. Decisions need to be made concerning which drugs are tested for, how often testing is performed, how much advance notice is given to athletes, who is informed of the positive test results, counseling options, penalty structure, and appeal process. Each one of these is an important component of a comprehensive drug-testing program, and failure to adequately consider them can reduce a program to little more than window dressing. For example, the parameters for an appeal should be narrowly confined to issues of chain of custody and analysis; WADA simply defines a doping violation as "the presence of a prohibited substance or its metabolites or markers in an athlete's bodily specimen."³¹

Finally, drug education and counseling should be considered a necessary part of any drug-testing program. At the very minimum, athletes have the right to be informed about the drug-testing program and the prohibited list. In addition, it is useful to place the drug-testing program in the larger context of drug use among athletes and educate them regarding adverse effects, consequences of use, and ethics of sports. The latter is often neglected, but the use of banned performance-enhancing drugs is unethical, and this should be clearly communicated. Fortunately, there are several comprehensive educational programs available, and institutions can access existing materials to develop their programs.^{10,11} Another omission in many drug-education programs is to focus only on the athlete. Education should also be provided to ancillary personnel including certified athletic trainers, coaches, and administrators. All of these groups are in a position to influence the athlete and are part of the larger circle of drug use.

CONCLUSION

The use of performance-enhancing drugs in sports has unfortunately necessitated that drug testing become an

integral part of athletics. Because of that, it is essential that the team physician have a thorough understanding of drug use among athletes and drug testing. Although drug testing has grown to encompass lawyers, administrators, and other personnel, there are significant medical aspects that require physician involvement. The one constant in the field of sports pharmacology is the ever-changing nature of the drugs and the methods of detection. Team physicians are often in an excellent position to observe these trends and help ensure healthy, ethical competition. Although physicians have frequently been part of the doping problem, they can also affect the solution by developing educational programs for athletes, identifying athletes in need of treatment, and assisting with drug-testing efforts.

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