ERGOGENIC DRUGS IN SPORTS

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The use of pharmacologic agents to improve athletic performance, or "doping," has been reported as early as the third century BC. "Doping" is described by the International Olympic Committee (IOC) as "the administration of or use by a competing athlete of any substance foreign to the body or any physiological substance taken in abnormal quantity or taken by an abnormal route of entry into the body with the sole intention of increasing in an artificial and unfair manner his/her performance in competition. When necessity demands medical treatment with any substance which because of its nature, dosage, or application is able to boost the athlete's performance in competition in an artificial and unfair manner, this too is regarded by the IOC as doping."[51]

Although there have been anecdotal reports of doping throughout history, it was not until the middle of the twentieth century that documentation of usage became more widespread. One of the reasons for this increased awareness of usage may be the fact that pharmacology has improved significantly. As more potent and effective drugs were developed, some athletes began to see the potential for artificially enhancing their own performance.

Legislation was prompted as rumors of ergogenic enhancement in sports increased. The IOC's Medical Commission was founded in 1967. One of their principal duties involved the investigation of possible drug

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misuse by athletes. Official drug testing of athletes began with the 1968 Olympic games in Mexico City. 31

Despite legislation and increased random testing, the use of pharmacologic agents has continued and actually increased. Reports now indicate that, even at the high school level, many athletes are using a variety of drugs to enhance performance. 3 These epidemiologic studies probably underassess the prevalence of drug use, given that their data are from self-reported questionnaires.

The goal of this article is to provide the practicing clinician with an account of the commonly used ergogenic substances used in doping by athletes. We will discuss these agents in the manner in which the IOC has developed their classification.

This article also focuses on doping classes and methods. Although the remaining topics are important, their ergogenic potential is limited. It should be noted that epitosterone has been used in the attempt to mask steroid use. Also, probenecid has been used to decrease renal excretion of banned substances. Local anesthetics, corticosteroids, and beta agonists may be used with certain limitations in some athletic events. The prescribing physician should be aware that restrictions exist and consult the appropriate organizing body.

DOPING CLASSES

Stimulants

Stimulants are used by athletes in the belief that they may reduce fatigue as well as increase alertness, response time, and strength. This category includes a variety of central nervous system stimulants as well as sympathomimetics.

Amphetamines

Amphetamines were first developed in 1920. Their vasoconstrictive properties were initially utilized for treatment of nasal congestion. The ergogenic qualities became more apparent during World War II, when amphetamines were commonly used by soldiers as a means of increasing alertness on patrol duty. 31 Although amphetamines are still commonly used today, studies have shown a decline in use between 1984 through 1988. 32

Structurally, amphetamines are similar to endogenous catecholamines, such as epinephrine. Their mechanism of action is believed to be augmentation of neurotransmitter release, especially norepinephrine, thereby stimulating the sympathetic nervous system. Their peak effect
is usually noted in 1 to 2 hours.\textsuperscript{18} Although there are conflicting reports as to whether athletic performance is enhanced by amphetamines, there may be a mild improvement in swimming or throwing sports, such as shot put.\textsuperscript{49} There are also some reports of prolonging the time to exhaustion, but there is no effect on actual speed.\textsuperscript{9}

In many studies, there does not appear to be an increase in overall capacity for aerobic activity, but there may be an increase in tolerance of strenuous exercise. The athlete may be able to prolong exercise time by blunting pain perception and the symptoms of fatigue and exhaustion. This decrease in ability to sense the body’s limitations may lead to an increased incidence of heat injury. Amphetamines also increase aggression, increasing the potential for injury in contact sports.\textsuperscript{42}

Side effects have included thermoregulatory difficulties, such as heatstroke. Neurologic symptoms include restlessness, tremor, irritability, insomnia, and increased aggressive behavior, as well as the potential for addiction. Cardiovascular effects include angina, dysrhythmias, headache, palpitations, changes in blood pressure, and changes in heart rate. Adverse gastrointestinal side effects include abdominal pain, vomiting, and decreased appetite. There have even been some reports of fatal ingestions with convulsions, coma, and cerebral hemorrhage.\textsuperscript{42}

Caffeine

Caffeine is a methylxanthine that occurs naturally in many species of plants, including coca, coffee beans, and tea leaves. It is also found in numerous cola drinks and chocolate. Caffeine acts through a variety of mechanisms. The most important central nervous system action is believed to result from its role as an adrenergic receptor antagonist. Other systemic effects may include increased muscle contractility from an increased permeability of the sarcoplasmic reticulum to calcium. Caffeine may also inhibit phosphodiesterases and potentiate the role of hormones as neurotransmitters.\textsuperscript{18} Generally, caffeine will have an effect on the central nervous system at a concentration of 85 to 200 mg. At this point, it will decrease fatigue and improve the level of consciousness.\textsuperscript{34} The ergogenic dose is believed to be between 250 and 350 mg.\textsuperscript{18} The IOC considers a urine concentration of greater than 12 \( \mu \text{g/mL} \) as consistent with doping. The National Collegiate Athletics Association’s (NCAA) defined limit is 15 \( \mu \text{g/mL} \). As an example of the quantity of caffeine that this represents, an athlete would need to drink six to eight cups of coffee in one sitting and be tested within 2 to 3 hours to reach the required urine concentration.\textsuperscript{51} Potentially, the amount of caffeine needed for the ergogenic benefits is far less than defined limits.

Studies with caffeine do not demonstrate an effect on large muscle groups in terms of strength and short-term performance; however, caf-
feine may improve endurance. In a study of nine cyclists, caffeine users were able to exercise 20% longer than in the control group. They also had significantly higher levels of plasma fatty acids and blood glycerol.\textsuperscript{11} The theory is that caffeine increases lipolysis while sparing glycogen.

Oxidation of fatty acids would then provide the initial energy source, leaving glycogen available for later use. Other studies have not reached the same conclusions.\textsuperscript{20}

Side effects include anxiety, irritability, restlessness, tremor, headaches, insomnia, diuresis, gastrointestinal disturbances, and tachycardia. These effects may occur after just a few cups. If used to excess, caffeine can be lethal at a dose of 3 to 10 g, causing seizures, tachycardia, or ventricular dysrhythmias.\textsuperscript{18}

\textbf{Clenbuterol}

Clenbuterol is a \(\beta_2\) agonist used in Mexico and some European countries as a bronchodilator, and it is available in both oral and aerosolized forms. The FDA has not approved its use in the United States. Clenbuterol came to public awareness at the 1992 Summer Olympics in Barcelona when an American hammer thrower, Jud Logan, and shot-putter, Bonnie Dasse, were disqualified after testing positive for this substance. This drug has been studied extensively in laboratory animals and livestock as a repartitioning agent.\textsuperscript{30} Reeds et al\textsuperscript{36} demonstrated that young rats fed clenbuterol showed an increase in the protein and RNA in skeletal and cardiac muscle, as well as a reduction in fat deposition and an increase in energy expenditure. Similar studies have been reported in livestock that support these results. Athletes have extrapolated the results of these studies in hope of gaining the anabolic as well as fat-reducing qualities of this and other \(\beta_2\) agonists.\textsuperscript{50} Di Pasquale\textsuperscript{13} states that if it does have an anabolic effect, relative to steroids it is weak. DiPasquale\textsuperscript{15} estimates that up to a third of elite athletes have tried this drug.

The mechanism of action has not been completely elucidated. Clenbuterol has been shown to cause skeletal and cardiac muscle hypertrophy, but not hyperplasia,\textsuperscript{40} even in denervated muscle.\textsuperscript{40} This occurs by suppression of both muscle synthesis and to a lesser degree muscle degradation, with the net result being muscle hypertrophy.\textsuperscript{50} Clenbuterol directly stimulates lipolysis as well.\textsuperscript{50} As a result of its lipolytic activity, it is currently being studied for use in obesity.\textsuperscript{49} Clenbuterol also causes sympathetic stimulation of \(\beta_2\) receptors, causing peripheral and central effects similar to those of other \(\beta_2\) agonists. Athletes generally use the oral form of this drug at a starting dose of twice that used in the treatment of bronchospasm (0.0172 mg/kg).\textsuperscript{50} Animal studies used doses of 0.33 to 2.0 mg/kg. Owing to rapid downregulation of receptors,
athletes often cycle clenbuterol, taking it on and off in 2-day cycles for 8 to 10 weeks, followed by 10 to 12 weeks without the drug.\textsuperscript{49} Clenbuterol has been used following the discontinuation of steroids to retard muscle mass loss and to aid in stripping subcutaneous fat for improved muscle definition.\textsuperscript{30}

No studies have been performed on the athletic population. Studies have been performed using albuterol in the inhaled and oral forms. Altogether, inhaled $\beta_2$ agonists appear to have therapeutically minimal influence on power, maximal oxygen consumption, work, and results of most respiratory function tests. This appears to be a result of the short half-life of inhaled albuterol.\textsuperscript{46} Studies of extended-release oral forms of albuterol have shown increased strength in hamstring and quadriceps musculature, which have a high proportion of type II fibers.\textsuperscript{29} As a result of these and other studies, no systemic use of $\beta$ agonists is allowed by the IOC, and clenbuterol is not permitted in any form.

Adverse effects are the same as for other $\beta_2$ agonists, including tremor, tachycardia, anxiety, palpitations, headache, nausea, anorexia, and insomnia. More serious side effects include cardiac muscle hypertrophy, dysrhythmia, and hyperthermia.\textsuperscript{35, 49}

\section*{Cocaine}

Cocaine is one of the most commonly used narcotics by athletes. It is found in the leaf of the coca plant and has been used in the past by South American Indians to ease the strain of their work at high altitudes. The proposed mechanism of action is by inhibition of the re-uptake of norepinephrine and dopamine at their respective postsynaptic sites.\textsuperscript{31} Modern use is reflected in a 1986 survey of the National Football League (NFL), which described it as the most commonly abused drug. This same survey suggested that use was more for recreation than as an ergogenic agent.\textsuperscript{18} Studies on cocaine/crack use demonstrated a dramatic decrease between 1984 and 1988, from 17\% to 5\%. Much of this is due to the potential for sudden cardiac death. During the same period, overall use of major pain medication did increase from 28\% to 34\%.\textsuperscript{52}

There have been no well-controlled studies regarding the ergogenic potential of cocaine. It is believed that low doses may act along a similar path to that of amphetamines.\textsuperscript{18} Users of cocaine report experiencing a "high" with increased alertness and feeling more mentally and physically powerful.

Cocaine affects the cardiovascular system by increasing cardiac activity and sensitivity, which may lead to hypertension, tachycardia, and even arrhythmias. Chronic rhinitis or septal necrosis may result from the nasal route of ingestion. The most dramatic side effect of cocaine use is sudden cardiac death. This has been reported in some
athletes by coronary occlusion. Cerebrovascular accidents have also been associated with cocaine use, possibly from sudden elevations in blood pressure. Smoked “crack” cocaine is even more dangerous. Given its increased rate of absorption from inhalation, cocaine’s effects on the cardiovascular system are intensified.

**Sympathomimetics**

Sympathomimetics are also used in the belief that they decrease fatigue and may enhance strength. They are generally synthetic drugs that mimic the sympathetic nervous system through activation of adrenoreceptors. The β₁ receptors trigger an increase in heart rate and ventricular force of contraction. β₂ receptors act to dilate bronchioles and coronary vessels. They are used in a variety of products. Ephedrine, phenylpropanolamine, and pseudoephedrine are found in over-the-counter asthma and cold medications. β₂ agonists are frequently used in treatment of asthma. Although the IOC has banned medications, such as albuterol and terbutaline in the oral form, they are allowed in aerosol or inhalant form.

Despite the wide availability and use of sympathomimetics, there are very little data on their efficacy. One controlled study demonstrated an increase in the exercise heart rate as well as a higher resting pulse pressure. A decrease in recovery rate following muscular effort was also noted. There were no significant effects on strength, endurance, power, or reaction time.

**Narcotic Analgesics**

Narcotic analgesics act on the central nervous system to depress fear, anxiety, concentration, and pain sensation. They include morphine, heroin, and other compounds of a similar chemical structure. All act by reproducing the effects of endogenous opiates, such as endorphins and encephalins.

The main ergogenic benefit is derived from the analgesic properties. Decreased pain perception allows athletes to exert themselves beyond their normal pain threshold. This may pose a hazard by encouraging competing despite an existing injury, and it may predispose the athlete to incurring even greater harm. There is strict legal control over most narcotics because of the high potential for addiction. The exception to this control is codeine, which is widely available in a variety of medicines, such as cough syrups and cold remedies. Generally, the levels of codeine in these medicines are too low to produce the adverse effects associated with narcotic analgesics; however, codeine may be detected
during drug testing because it is metabolized along a similar path as for morphine.

Narcotics are infamous for their ability to cause tolerance and dependence, but no well-controlled studies have been performed to evaluate their ergogenic capabilities. Common side effects include dry mouth, pupillary constriction, pruritus, and respiratory depression. Most cases of fatal overdose are secondary to respiratory distress. Withdrawal symptoms after habituated use include restlessness, nausea, vomiting, diarrhea, and muscular cramps.

**Anabolic-Androgenic Steroids**

Anabolic-androgenic steroids are testosterone derivatives that exert anabolic (tissue building) and androgenic (masculinizing) influences on the body. In this discussion of anabolic-androgenic steroids, the terms anabolic steroid and steroid will be used interchangeably.

Since ancient times, humans have searched for substances that promote an anabolic effect. In 1889 Brown Seuqard tested bull testicle extract and claimed it had anabolic effects and gave other health benefits. As late as the 1920s, physicians transplanted primate testicles in humans to restore sexual function and vigor to aging men. In 1935, testosterone had been isolated and chemically characterized, and the nature of its anabolic effect elucidated. In the same year, an oral preparation became available, and it was immediately used clinically. In the late 1930s, different testosterone derivatives, both oral and parenteral, were formulated in an attempt to separate the androgenic and anabolic qualities of these substances. To date, it has not been possible to separate these characteristics. In 1939, the Bulletin of the Health Organization of the League of Nations stated that testosterone and its derivatives may enhance performance in sport. In 1941, Holloway, a racing horse, was shown to dramatically improve his performance after using testosterone, and by 1950s the Soviet power lifters initiated the use of steroids in sport. In 1954, Dr. Ziegler, the team physician for the US power lifting team, traveled to the Soviet Union and began using anabolic steroids on himself and the US weightlifting team. At the 1964 Olympics, anabolic steroids were used extensively by the Soviet and US athletes, and by 1968, use had spread to many sports. In 1968, Waddell estimated that one third of all track and field athletes were using these drugs, and in the 1972 Olympics in Munich, testing of nonsteroidal drugs was initiated, with users penalized, but it was not until the 1976 Olympics in Montreal that testing for steroids was initiated. The use in women began in the 1950s in the Soviet Union, and by the early 1970s, the US women were using them as well. In football, Alvin Ray, the power-lifting coach
for the San Diego Chargers and former US power-lifting coach, introduced anabolic steroids to the National Football League. In college football, use was widespread by the late 1960s, and the NCAA banned their use in 1973.94

As early as 1959, use by high school athletes was rumored to be occurring.17 More recent studies have evaluated the incidence of use in various groups. In 1987, Buckley and coworkers6 found that 7% of male high school seniors had used steroids, and more than a third of these users were not involved in interscholastic sports.6 At least 11 US state and local studies found that 4% to 12% of high school boys and 1% to 2% of girls had used steroids.59 At the college level, Anderson and colleagues83 performed three studies in 1985, 1989, and 1993 involving 11 universities from divisions I through III, and their numbers fell within the preceding ranges. Yesalis56 in 1990 employed a projected response survey in collegiate athletes. Football had the highest rate of use at 29%, with men’s track at 21%, and women’s track at 16%. At the elite level, a study of athletes in the 1972 summer Olympics showed a lifetime use of 68%, with 61% using steroids over the previous 6 months. At the recreational level, a study of weight lifters in three Chicago gymnasiums reported that 44% had used anabolic steroids on at least one occasion. Based on data from the National Household Survey on Drug Abuse, there are more than one million current or former users, 300,000 users within the past year, and a median age of 18 years for initial usage. Among the 12- to 34-year age group, there was a positive association with the use of other illicit drugs, alcohol, and cigarettes.58 Multiple survey studies have been performed with variable results. The problems associated with self-reporting surveys, such as under-reporting bias and fear of prosecution, may explain these differences. Further studies will more clearly establish the true incidence and prevalence of steroid use in groups.

Owing to the widespread abuse of anabolic steroids, in 1990 President Bush signed into law the Anabolic Steroids Control Act, making the illicit distribution of these substances a felony and adding these drugs to Schedule III of the Controlled Substances Act.

Anabolic steroids increase protein synthesis. They also decrease the catabolic effect of naturally occurring glucocorticoids by competing for their receptor sites. The central nervous system effects occur through increases in acetylcholine and monoamine and peripherally by increasing acetylcholine at the neuromuscular junction.24 During the past 50 years, anabolic steroids have been used in various reproductive dysfunctions, anemia, hereditary angioedema, metastatic breast cancer, depression, psychoses, and protein deficiency states, as well as in patients convalescing from severe infections, surgery, burns, and trauma. In 1990, the American Medical Association (AMA) listed specific clinical uses for
anabolic-androgenic steroids including the following: hypotestosteronemia, anemia, metastatic breast cancer, hereditary angioedema, endometriosis, and fibrocystic breast disease.

More than 40 anabolic-androgenic steroids are on the market today. Oral, parenteral, and transdermal forms are available in the United States, and intranasal forms are available in other countries (Table 1). Although most of these drugs are obtained through the “black market,” it is estimated that 10% to 15% of them are obtained by prescription.

Athletes use many regimens to maximize their steroid effect. All of these are learned from their peers or coaches. The physician should be cognizant of the vocabulary used for these drugs. Continuous dosing means the athlete never stops the use of steroid, whereas in cycling the athlete has some time off of the drugs to prevent plateauing or tolerance. The average cycle lasts from 6 to 12 weeks. Stacking means that more than one anabolic steroid is used at a time, usually with staggered cycles of the individual drugs. Pyramiding is a gradual increase in dosage, with a gradual taper after maximum dosage is attained, whereas an array is the use of multiple drugs to counteract side effects or to enhance the effect of the steroids. These drugs include tamoxifen, levothyroxine, diuretics, high-dose potassium supplements, growth hormone, and human chorionic gonadotropin.

Endurance athletes use anabolic steroids primarily for their catabolism blocking effects, allowing increased training and more rapid recovery. They generally use doses at or below physiologic levels (7 mg/day in men). Sprinters use them to increase strength and power and to improve recovery, and they generally use doses one to two times greater than physiologic doses. In strength sports, it is not uncommon to use

Table 1. COMMONLY USED ANABOLIC-ANDROGENIC STEROIDS

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<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Derivative</th>
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<tr>
<td>Oral</td>
<td>Ethylestrenol</td>
<td>Maxibolin</td>
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<td></td>
<td>Fluoxymesterone</td>
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<td>Methandrostenedione</td>
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<td>Methyldienandrostenedione</td>
<td>Metandren, Oreton Methyl</td>
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<td></td>
<td>Oxymetholone</td>
<td>Anadrol-50</td>
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<td></td>
<td>Stanazolol</td>
<td>Winstrol</td>
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<tr>
<td>Injectable</td>
<td>Nandrolone</td>
<td>Deca-Durabolin</td>
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<tr>
<td></td>
<td>Nandrolone phenylpropionate</td>
<td>Durabolin</td>
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<tr>
<td></td>
<td>Testosterone cypionate</td>
<td>Depo-testosterone</td>
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<td></td>
<td>Testosterone propionate</td>
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<td>Testosterone enanthate</td>
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<td>Transdermal</td>
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<td></td>
<td>Testosterone</td>
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10 to greater than 100 times physiologic doses. Women, regardless of sport, are generally thought to use lower doses than do men.

Although the vast majority of the athletic community accepts that anabolic steroids improve exercise capacity and performance, the extent to which this occurs and the factors influencing such effects remain incompletely understood and documented. Studies in healthy young male animals have shown equivocal effects, but animals with lower natural hormone levels than in young men, such as castrated males, females, and old animals, often show substantial increases in muscle mass with steroid use. In endurance sport, anabolic steroids have been shown to increase erythropoiesis, therefore potentially improving aerobic capacity. They have also been shown to have an anticatabolic effect, allowing increased exercise tolerance, intensity, duration, and frequency of training. Another important effect is the decrease in recovery time, which is advantageous to the athlete. In strength and power sports, anabolic steroids have been shown to increase lean mass and decrease fat percentage in the well-trained athlete. There seems to be little advantage to the unconditioned individual. In 1984, the American College of Sports Medicine presented a position statement regarding anabolic steroids: "Anabolic-androgenic steroids, in the presence of an adequate diet, can contribute to an increase in body weight, often in the lean mass compartment. The gains in muscular strength achieved through high-intensity exercise and proper diet can be increased by the use of anabolic-androgenic steroid in some individuals."

It was believed until recently that the use of anabolic steroids was associated with multiple and sometimes life-threatening adverse reactions, but with the extensive use by athletes, few problems have occurred. The short-term health effects of anabolic steroids have been increasingly studied and reviewed, and although anabolic steroid use has been associated with several adverse and even fatal effects, the incidence of serious effects thus far reported has been extremely low. The long-term effects of anabolic steroid use are generally unknown.

It is documented in multiple studies that the 17-alkyl androgens (oral forms) have a profound effect in altering lipids. The lowering of the high-density lipoprotein (HDL) is greatest, with a less significant increase in low-density lipoprotein (LDL) and triglycerides; it is not known what long-term effect this has on the athlete, but prolonged use would suggest an increased risk of cardiac disease. Animal studies have shown that collagen abnormalities occur. Male pattern baldness and acne are also increased. Gynecomastia is a common effect, resulting from peripheral conversion of the androgen to estradiol. There is minimal effect on blood pressure, and the effect on glucose metabolism is equivocal. The risk of HIV and hepatitis A and B is great with needle sharing. In one study, 25% of adolescent steroid users reported needle
sharing. There is a definite association of the 17-alkyl androgens (oral forms) with peliosis hepatis, cholestatic jaundice, and hepatocellular adenoma. There have been deaths associated with necrosis and rupture of the tumor or the cysts in peliosis hepatis. Portal hypertension can occur in peliosis hepatis. Several case reports of hepatocellular carcinoma have been associated with anabolic steroid use, but a true association has not been demonstrated. Temporary infertility is also associated with steroid use.

With steroid use there have been individual case reports of the following: myocardial infarction, cerebrovascular accident, prostate cancer, testicular atrophy, cardiomyopathy, Wilms’s tumor, lymphoma, colonic adenocarcinoma, and bleeding esophageal varices. Psychological changes associated with anabolic steroids have been documented and include increased aggressiveness, depression, mania, psychosis, and increased libido. Many studies have been performed with conflicting results. Psychological dependence has also been documented, and it is suggested that physical dependence may occur in some instances via opiate receptors.

Side effects specific to women deserve special mention. Reversible changes include the following: menstrual abnormalities, increased libido, breast atrophy, acne, and increased aggressiveness. Irreversible changes are the following: facial hair growth, extension of pubic hair, hypertrophy of the clitoris, deepening of voice, and loss of scalp hair.

As physicians, we have discouraged anabolic steroid use, warning the athlete that they are dangerous drugs used only with great risk, but their peers have used these drugs for extended periods of time with no apparent consequences. As a result, our reputation as the athlete’s advisor has suffered tremendously. In discussing anabolic-androgenic steroids, we hope that this information can allow the reader to convey the true risks and benefits to the athlete so he or she can make an informed decision regarding the use of anabolic steroids and the other drugs discussed.

**Beta-Blockers**

Beta-blockers are commonly used in conditions affecting the cardiovascular system. They act primarily to decrease heart rate, cardiac output, stroke volume, and mean arterial pressure. As such, they have been of tremendous benefit in treating hypertension, as well as after myocardial infarction. In sporting events, beta-blockers are used when a calming effect is required, such as during shooting events for archery. Beta-blockers would tend to hinder maximal performance in events that require an increase in cardiac response. As such, they are not used for
endurance or aerobic activities. The main benefit is believed to be by reducing anxiety and alleviating tremors. Some have suggested that this benefit may be more of a factor for those with less experience. Negative side effects include bronchospasm, heart failure, heart block, aggravation of peripheral vascular disease, impaired glucose control in diabetes mellitus, fatigue, and a decreased ability to perform endurance activities.

**Diuretics**

Diuretics are generally used in medicine for the elimination of excess fluid from the body. Athletes can obtain benefit from this property in two primary fashions. The forced loss of body fluid can bring about a rapid decrease in weight. This would be of definite advantage in sports in which competitors are matched by weight divisions, such as in boxing, weightlifting, or wrestling. Diuretics have also been used by competitors to increase urine production at times when they are likely to undergo drug testing. The belief is that an increase in urine volume will dilute the doping agent; however, given the specificity of drug testing, using techniques, such as immunoassay, chromatography, and mass spectrometry, this type of masking is not likely to be effective.

**Growth Hormone**

Human growth hormone (hGH) is a polypeptide hormone produced and stored in the anterior pituitary gland. Animal breeders in the 1930s discovered that animals given extract from species-specific pituitary glands developed increased muscle mass, decreased body fat, and an accelerated growth rate. Researchers in the 1950s realized that hGH stimulated the production of somatomedins, which increased growth. Soon thereafter, hGH was used in humans for growth hormone deficiency in children and in Turner’s syndrome to promote normal growth. In 1985 two forms of synthetic growth hormone were produced. One form was identical to the human hormone and the other differed by one additional amino acid. Antibody production was quite high in these early preparations. Prior to this advancement, hGH was derived from cadaveric specimens. This resulted in cases of Creutzfeldt-Jakob disease in recipient.

With improved drug testing techniques in the 1980s, anabolic steroid usage was more easily detected. As a result, athletes turned to other substances that mimicked the benefits of anabolic steroids but were not detectable by current drug testing methods. The prevalence of the use
of hGH is unknown because it is undetectable, but its use is common particularly in bodybuilding and football. Growth hormone exerts its effect on all cells of the body. Skeletal and soft-tissue growth is stimulated. Glucose intolerance and lipolysis occur, and protein synthesis is increased. Increased protein deposition occurs from facilitation of nearly all aspects of amino acid uptake and protein synthesis by the cells, with concurrent reduction in protein catabolism. The GH-mediated growth is different from the growth that occurs as a result of work. New RNA must be synthesized for exercise-induced muscle growth, whereas GH-mediated growth occurs as a result of increases in the rate and translation of already existing RNA. In a series of animal experiments, Goldberg concluded that GH increased the basal metabolic rate of protein synthesis, but that protein synthesis was also determined by the amount of muscular work. It is difficult to predict the ability of GH to increase the contractile elements and improve the performance of normal muscle in normal humans.

The therapeutic use of growth hormone is for increasing the stature of growth hormone–deficient children, in Turner’s syndrome, and for some short-statured children. Little information exists on the use of hGH in athletes, although there have been reports of athletes using 20 times the therapeutic dosage. The therapeutic dose is 0.06 mg/kg (1.5 mg/day) three times per week by the intramuscular route. The cost of an 8-week supply was estimated at $1000 to $1500.

Athletes use this drug to enhance definition and to increase the size and strength of muscle. It is not yet known whether these potential benefits to athletes occur. No studies have been done that demonstrate significant increases in performance in athletes. The studies reviewed consistently demonstrate an increase in lean body mass with a decrease in fat percentage. For example, Christ et al studied the effects of hGH on body composition. Following 6 weeks of hGH administration, resistance exercise, and a high-protein diet, there was a significant increase in fat free weight and a decrease in fat percentage compared with the placebo group; performance was not studied. More studies must be performed to determine if there is truly an ergogenic benefit with the use of hGH.

Known adverse effects of hGH include acromegaly, antibody formation, hypothyroidism, hypercholesterolemia, coronary artery disease, congestive heart failure, cardiomyopathy, myopathies, arthritis, diabetes mellitus, impotence, osteoporosis, menstrual irregularities, and Creutzfeldt-Jakob disease. “Black market” sources of hGH often include the former Soviet Union. These products are still derived from cadaveric specimens. Creutzfeldt-Jakob disease is a real and significant risk when using black-market hGH because it is produced from cadaveric specimens and sold as recombinant hGH. Acromegaly occurs in patients at
concentrations of 5 to 30 ng/mL, which is equivalent to 1.5 to 9 mg/day. As little as twice the therapeutic dose may result in acromegaly. This dosage is generally exceeded by athletes, and the potential for developing acromegaly and other adverse effects of growth hormone is significant. It is probably the prohibitive cost of hGH that prevents the frequent occurrence of these effects.

Other Peptide Hormones

Human chorionic gonadotropin (hCG), leutinizing hormone (LH), adrenocorticotropic hormone (ACTH), gonadotropin-releasing hormone (GnRH), corticotropin-releasing factor (CRF), and growth hormone releasing-hormone (GHRH) are now available owing to advances in recombinant DNA. hCG has identical biologic effects as for LH, and it is used by athletes to stimulate endogenous sources of testosterone production without disrupting the natural testosterone-to-epitestosterone ratio. LH is apparently not used by athletes owing to the greater availability of hCG. When assays are developed, LH levels can be used to indirectly identify anabolic steroid users. ACTH has no ergogenic benefit and is, in fact, detrimental to athletic performance. GnRH and CRF, if administered exogenously, cause rapid downregulation of hypothalamic receptors, and they are, therefore, ineffective in enhancing performance. GHRH administered exogenously does increase hGH levels and has potential for abuse. At the present time, no assays can effectively detect the use of these substances in the athlete, but because of their anecdotal increase in use by the athletic community, the Medical Commission of the IOC is supporting the development of these assays.24

BLOOD DOPING

It has long been noted that an athlete's performance in endurance events improved after long-term training in a high altitude. As the body produces more red blood cells, there is an increase in arterial oxygen concentration and delivery capabilities. This improved oxygen delivery to skeletal muscle would enhance endurance capabilities during exercise. Rather than undergo the physical inconvenience and time required to acclimate to altitude, it was hypothesized that artificial hemococoncentration by red blood cell infusion might have a similar ergogenic effect. The first such documented use occurred in the 1976 Olympic Games in Montreal.18

The blood used may be drawn from the same individual (autologous) or from a different donor (homologous), which has been type
matched with the recipient’s blood. Generally, two units of blood are removed and preserved by freezing at ~80°C. The athlete’s body then compensates for this relative anemia with production of new red blood cells, restoring a normal hemoglobin and hematocrit. The previously frozen blood is then thawed and re-infused at 1 week before competition. The efficacy of blood doping has been substantiated with studies.22

Post-transfusion hemoglobin should be less than 17 g/dL, and the hematocrit should be less than 50%.40 Otherwise, a hyperviscosity syndrome may develop. This involves an elevation in blood viscosity, leading to decreased blood-flow velocity. This could progress to a decreased cardiac output with intravascular clotting, potential heart failure, and death. Thrombosis could be manifest as cerebrovascular accidents, myocardial infarction, pulmonary embolism, or deep vein thrombosis. Also, with any transfusion, there is risk of infection. With homologous transfusion, mismatch in blood typing can also lead to potentially fatal hemolytic reaction and renal failure, allergic reactions, and contracting of infectious diseases such as viral hepatitis, malaria, cytomegalovirus, or HIV.42

ERYTHROPOIETIN

Erythropoietin (EPO) is a compound that is naturally produced by the kidney to stimulate red blood cell production by the bone marrow. This, in turn, leads to an increase in the red blood cell mass and the hemoglobin and hematocrit. Purified EPO was first isolated from human urine in 1977. By 1985, the gene that codes for EPO was cloned, and soon after recombinant human erythropoietin (rHuEpo) became available. Its half-life varies depending on the route of administration, with 20 hours being the longest when administered subcutaneously. Red cell production will continue for as long as 2 weeks; however, rHuEpo is used mainly to treat anemia caused by renal disease.52

To the advantage-seeking athlete, this compound may provide all the benefits of blood doping, without the risks involved in blood transfusion. Equivalent effects on performance in endurance activities would seem likely, but they currently are unproved.40 Although the athlete is at decreased risk for transmission of infectious disease or transfusion reactions, there are still potential hazards. Increased hemoglobin and hematocrit could result in hyperviscosity of the blood, with many of the same risks as seen in blood doping.52

Currently it is impossible to identify rHuEpo by drug testing. rHuEpo is virtually identical to the endogenous protein and is excreted in the urine in an amount that is too small to be tested. Also, it is rapidly
metabolized, and its effects extend far beyond any test’s capability to detect.32

CONCLUSION

Given the competitive nature of sports, athletes will always seek advantage over their opponents. Unfortunately, some of these athletes will resort to using ergogenic aids. This usage is usually done in secret, with users not wanting peers, coaches, or physicians to be aware of their activities. As such, athletes are frequently misinformed and do not have accurate information regarding the methods they are using.

It is the physician’s responsibility to help maintain the safety and health of the athletes with which he or she works. The physician should remain vigilant for signs of doping. Suspicion should be aroused when there are physical changes that involve rapid gains in size and strength, leading to sudden, erratic improvements in performance. Behavioral changes, such as mood swings, aggressiveness, hostility, and irritability, may also be indicators of possible ergogenic use. By maintaining knowledge of current drugs and their effects, the physician will be able to recognize potential use of agents and intervene if necessary. Providing athletes with information about the efficacy, side effects, and policies concerning drug use may help the athlete make an informed decision regarding the use of these substances.

If questions arise, various resources are available. The US Olympic Committee has a drug-testing program that mirrors the IOC’s program. An official list of banned substances can be requested from them. They also provide a toll-free, confidential telephone hotline to answer questions relating to banned substances (800-233-0393). The National Collegiate Athletic Association also provides a toll free number for their prohibited substances (800-546-0441).41

References


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