

Erythropoietin and athletes

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Erythropoietin and Athletes Steven D. Jackson Student, American Military University Abstract Erythropoietin (EPO) use as a performance enhancing agent in sport carries both significant and detrimental risks to go along with its suggested benefits. As such, it was banned by the International Olympic Committee in 1990. Shortly thereafter, successful and reliable testing methods have been developed to test athletes for its potential use.

Despite widespread knowledge of its potential adverse effects and the testing for its attempted use, EPO use remains substantial amongst endurance athletes of nearly all ages and disciplines, both professional and amateur. This paper will provide a history of EPO as a performance enhancing substance, explain its associated risks and perceived and actual benefits, attempt to analyze why athletes feel compelled to use it, and examine the sanctions, regulations, and weighty repercussions associated with its use. Erythropoietin and Athletes

In sport, there are a virtually limitless number of ways in which one can influence or positively impact physical or mental performance. These methods can come in the form of mechanical aids, pharmacological aids, physiological aids, nutritional aids, and psychological aids. Regardless of its source, any means by which one seeks to improve performance by enhancing the physiological capacity of a particular system of the body, removing psychological constraints which adversely affect performance, or by accelerating recovery from training or competition is called an ergogenic aid (MacKenzie, 2001).

These may include something as simple and innocuous as a healthy meal consumed the night prior to a competition, but seemingly, the ergogenic aids

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which athletes are turning to more increasingly are those that have been banned by organizations such as the World Anti-Doping Agency, the International Olympic Committee, and the like. Often, these substances have been banned because they not only represent perverse and unethical behavior, but also, as is the case for a substance like recombinant erythropoietin, because they can have serious adverse health effects for their users. Over time, these substances have changed, but the desire to gain an unfair competitive advantage remains. Hematopoiesis is the process which involves the production of mature cells in the blood and in lymphoid organs. Mature erythrocytes, or red blood cells, have no nucleus, so they cannot reproduce in the traditional fashion as other cells can. Erythropoiesis, then, is the process by which erythrocytes are produced. Erythropoietin is a naturally occurring hormone found within the human body which controls this red blood cell production.

It is released by the kidneys, and to a lesser extent the liver, and in very little quantities in the brain in response to a negative feedback. The physiological stimulus of erythropoietin production is hypoxia, or prolonged oxygen deficiency in body tissue, and in the majority of instances is related to the number of circulating erythrocytes within the kidneys. At high altitudes, for example, where the pressure oxygen in the air is reduced, oxygen delivery to the body's tissues initially decreases.

This drop in oxygen triggers the release of erythropoietin, which travels via the blood to the red bone marrow and stimulates red blood cell production (Shier, Butler, & Lewis, 2011). This is important to note, as this negative feedback of loss in oxygen is essentially no different than the body observing

a loss in blood, which also necessitates the release of erythropoietin. In cases of hemolysis or hemorrhage, erythrocyte production will also increase rapidly and substantially for the body to attempt to accommodate for the amount of blood lost.

However, overproduction of erythrocytes does not occur, both in extreme hypoxic environments and even after the most severe loss of erythrocytes (Robinson, et al. , 2006). This balance is very important, because adequate oxygen delivery to tissues depends on having a sufficient number of red blood cells to transport oxygen. Decreases in their number or function can hinder oxygen delivery and thus affect exercise performance. Red blood cells serve a primary function of facilitating this transport of oxygen, which is bound to the hemoglobin found in red blood cells.

Hemoglobin contains iron, which binds oxygen. As such, the oxygen-carrying capacity of blood is determined by its hemoglobin content. Accordingly, when hemoglobin levels fall, exercise performance is subsequently impaired. Being familiar with this, athletes, trainers, and coaches often practice iron supplementation in an effort to prevent anemia and attempt to boost hemoglobin levels. However, this supplementation cannot boost the blood's oxygen carrying capacity beyond that which is normal.

Consequently, doctors, trainers, and athletes have come up with various alternative means to try to boost blood's oxygen-carrying capacity, and in turn boost performance (Mottram, 2011). In traditional medical settings, the need for a means to raise red blood cell counts in patients suffering from kidney failure in order to alleviate their extreme anemia, as they have so few red blood cells that they typically experience near-permanent exhaustion.

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The demand for a way to treat these kidney patients precipitated the development of synthesized erythropoietin.

There was no question that they needed red blood cells, and the proposition of providing them via erythropoietin seemed logically safer than the more natural and traditional repeated transfusions and dialysis. The same logic applied to the much larger number of people whose kidneys were weak or damaged, but not yet failing. Raising their red blood cell count, and subsequently their hemoglobin levels, up to a normal amount like the more attractive option, and it was only a matter of time before it could be discovered (Burch, 2011).

In 1985, the gene responsible for the synthesis of erythropoietin was successfully cloned for the first time. This synthesized erythropoietin is known as recombinant erythropoietin, and first became available in Europe in 1987 and was later patented by Amgen in 1989 (Mottram). With this development, it quickly became evident that recombinant erythropoietin would be used illegally as a performance enhancer in endurance sports. As such, the International Olympic Committee elected to ban this drug in 1990, even though all forms of blood doping had been officially banned since 1984 (Robinson, et al.).

In its earliest clinical trials, recombinant erythropoietin proved very successful, and it was quickly put to use with patients requiring their hemoglobin be raised to normal levels. The trials showed the drug's benefits outweighed its risks, but not by much. In 2005, researchers and kidney specialists concluded their trials ahead of schedule when they were stunned by what they found. After years of raising red blood cell counts in patients to

normal healthy levels, which also raised their hematocrit—the proportion of red blood cells to total blood volume—doctors were not seeing decreased occurrences of stroke, heart complications, and even death. These rates were actually increasing. Therein laid the problem with EPO use, especially in uncontrolled environments and when used by athletes (Burch). Before EPO's adverse effects were widely known, and to a great extent even today, its proposed benefits led to its immediate abuse by endurance athletes. The first cases were reported in several newspapers within the four years after recombinant EPO appeared in Europe. These articles claimed a link between rumored EPO abuse and the deaths of 18 Belgian and Dutch cyclists.

This unfortunate wave seemed to roll on for some time, seemingly striking hardest amongst in the sport of cycling, and often resulting in death. For some time, cyclists publicly denied using EPO, but at the 1998 Tour de France, a masseuse for the Festina team was caught with EPO and several other banned drugs. The entire team and its staff were ejected from the Tour, and eventually seven of the nine Festina riders admitted to doping. Even the winner that year, Marco Pantani, was ejected the following year for signs of EPO use in an earlier drug test (Eichner, 2007).

Though the bulk of EPO use reported in the media comes from cycling, other sports are not free from it. Chinese runners, swimmers, and rowers, Russia's top female cross-country skiers, Finland's top skiers, and Germany's top runners all have been caught for suspected EPO use of some kind or another. Russian and American runners and sprinters, including American sprinter Kelli White, have been stripped of medals and handed bans for their admitted EPO use after failing drug tests.

Even Lance Armstrong—who has always denied any EPO use—has been suspected of illegal EPO use brought about by claims of his former teammates (Eichner). Perhaps the greatest contributing factor for the prevalence of continued illegal EPO use is in its difficulty of detection. While some athletes may think that they are using a drug for which there is no means of detection, which is not the case, others may simply know that EPO can be a very elusive drug to detect.

Early detection strategies for EPO use as a drug were limited to blood testing only. Though blood tests could confirm inconsistent hematocrit levels and other blood markers compared to base samples in athletes who may have been using EPO supplementation up to, and sometimes over, a week prior, or those that had been using EPO when they originally provided a base sample and had discontinued its use, a direct method for detection in urine had yet to be established.

Furthermore, early attempts at developing a urine test proved to be expensive, overly sensitive, and unreliable. Since blood doping had been common practice in some endurance sports for decades due to its clear performance advantages, it regrettably became even more attractive once recombinant EPO became available. Athletes have exploited these limitations of testing, particularly in sports that relied solely on urine specimen testing (Robinson, et al. . Successful urine testing had finally been developed and came into the picture in 2000. Serving as the only direct method of recombinant erythropoietin detection approved by the Court of Arbitration for sport, this method utilized electrophoretic techniques to separate the isoform profiles of recombinant and endogenous erythropoietin

found in urine according to their isoelectric points (Diamanti-Kandarakis, et al. , 2005).

Not only could this newly approved testing mathematically and scientifically identify EPO use—or discontinuation of its use—but it could also isolate the various forms of forms of EPO, including erythropoietin alpha, beta, omega, and delta, as well as newer generations of EPO analogues like darbepoetin and mimetic peptides. The disadvantage of such an effective urine testing method, however, was that it discouraged athletes from recombinant EPO use. Athletes now fearful of getting caught moved back to using—or rather misusing—blood doping and transfusions in an attempt to raise hematocrit and hemoglobin levels.

For that reason, some international sports federations elected to limit their testing to either blood or urine. However, more recently the trend has been to attempt to keep their current testing procedures randomized (Robinson, et al.). The risks of illegal EPO use remain high. Some athletes choose to supplement with EPO in smaller doses with the intent of limiting their potential exposure in drug tests, and, just as likely, with the expectation that this practice would be “ safer. Regardless, the results of EPO use are largely unpredictable, and tests have revealed that hematocrit values in EPO users can greatly exceed what is considered the healthy or normal upper limit of 50 percent. Once the hormone has been put in the body, the athlete is at great risk for substantial increases in blood viscosity. This places the individual in danger of thrombosis, myocardial infarction, congestive heart failure, hypertension, stroke, and pulmonary embolism. However, with the ever-increasing pressures to excel in competition, and the draw of larger

rizes, purses, sponsorships, and notoriety in sport today it is not beyond reason as to why teams, athletes, trainers, and coaches would feel compelled to explore an option which may offer athletes a clinically documented six to eight percent increase in their VO₂max and 13 to 17 percent increased time to exhaustion (Kenney, Wilmore, & Costill, 2012). Athletes who use banned EPO also risk disqualification from a particular competition, with the risk apparently greater if the athlete's result is good, as the top-placing finishers in competitions almost certainly are subject to testing more and more frequently.

They can also be banned from their sport, typically for a minimum of a year, but potentially for life. In their quest for enhanced performance, athletes can easily get caught up in the hype surrounding these sorts of substances and the purported benefits they might bestow. Unfortunately, too many athletes are blinded by ambition and do not consider the consequences of their actions until their careers have become jeopardized or their health has been seriously affected.

Considering recent reports of even amateur athletes being dealt bans and imposed fines after testing positive for EPO use in events that are considered recreational, the need is definitely present for the likes of the World Anti-Doping Agency and the International Olympic Committee to take more aggressive and decisive action in the battle against doping and illegal drug use. The misuse of medical and biotechnological advancements to enhance athletic performance is an issue that will clearly not go away on its own.

It is imperative for sports federations to be able to collect blood samples from their competitors and institute a continuity system which keeps track of

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appropriate individual values. The appropriate way to fight blood doping and EPO use is to markers for each individual athlete to have a record of each marker and measure of their blood. In this way it will not be necessary to take into account complicating factors during testing and analysis such as sex, ethnic origin, and the kind of sport in which the athlete is participating.

With a system such as this, it would be possible to identify which athletes are manipulating their bodies based on their own set reference values and markers over time. This, combined random, unannounced testing is the only way currently possible to effectively mitigate doping. Even still, it is supremely difficult for sports organizations and control agencies in sport to stay ahead of the always sophisticated doping methods. Summary Erythropoietin and all of its forms were developed with the intent of rehabilitating and alleviating the extreme symptoms of kidney patients.

Their appeal is strong to competitive athletes, especially with more and more on the line each year. Despite their undeniable ability to enhance performance, EPO can cause serious negative health effects. In an era where performance-enhancing drug abuse is rampant across nearly all disciplines of sports despite rigorous legislation and testing throughout the world, it is necessary to understand the harmful effects of all substances when considering their use.

The undesirable effects of EPO use are virtually countless, but—and perhaps worse yet—the potential long-term effects of chronic use are not well known.

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