The Evolution of Performance-Enhancing Drug Use in Sport

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Introduction

Although the use of drugs in sport can be traced back to ancient Greece, the modern history of the use of performance-enhancing drugs (PEDs) begins in the late nineteenth century in connection with emerging professional endurance sports such as 5- and 6-day cycling events, long-distance swimming and horse and dog racing. Commonly used drugs at that time were caffeine, cocaine, alcohol and strychnine, which were used either individually or in combination. By the 1920s, there was growing awareness and concern among sport organisations with regard to drug use, and between 1910 and 1920, scientists were beginning to develop detection methods for some drugs, initially those involved in horse racing [1]. International federations (IFs) were also beginning to amend their rules to address the emerging problem of doping. One of the first IFs to amend their rules was the international federation for track and field (International Amateur Athletic Federation, IAAF) who in 1928 prohibited the use of stimulants. However, as there was no reliable test for stimulants, the prohibition was largely ineffective. Between the 1920s and the 1960s, an increasing number of IFs and major event organisers amended their rules to prohibit doping, but just as simply amending rules had little effect unless there were reliable tests available, it was also true that the availability of reliable tests also had little impact unless there was a process and funding for conducting the tests and for the laboratory analysis.

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The 1950s and 1960s: The Spread of PEDs Use in Sport

The two groups of substances that were to become the main PEDs used by doping athletes were stimulants and steroids. The stimulant amphetamine was first synthesised in the late nineteenth century, and testosterone (the base compound for the development of synthetic steroids) was first isolated in the mid 1930s [2]. However, it was not until the 1950s and 1960s that evidence of the extent of their use in sport began to emerge. Three factors were particularly important in stimulating PED use in sport in the 1950s: first, scientific experimentation during the Second World War with drugs designed to keep soldiers alert and increase their aggression; second, the increasing success in the synthesis of drugs; and third, the deepening of the Cold War. The use of amphetamines by soldiers during the Second World War not only stimulated scientific research into stimulants but perhaps more importantly made the performance-enhancing properties of the drugs widely known among athletes and the general public. Evidence of extensive use of stimulants first appeared in cycling. According to Müller (2010), "In a cycling competition in 1955, five samples out of 25 tested positive for amphetamine … During several high-level cycling competitions (e.g., World Amateur Championship, Professional Cycling World Championship Zürich, Austria Tour) numerous cyclists (e.g., from Austria, the Netherlands and Poland) tested positive …" [2]. Also in the 1950s, evidence of the increasing use of anabolic agents across a range of sports was emerging although there were significant challenges in distinguishing exogenous consumption of anabolic androgenic steroids from normal endogenous production. The entry of the Soviet Union to the Olympic Games in 1952 intensified the ideological rivalry with the USA and provided a powerful legitimation for increased experimentation and use of PEDs in both countries. However, it is clear that experimentation and use of PEDs in the 1950s and early 1960s was not confined to the two major powers but was evident across a wide range of countries including England, Italy, France and Belgium and was also evident in a wide range of sports including cycling and rowing [3], football [4] and swimming [5]. Also of considerable significance was the early evidence that the doping practices of elite level athletes were moving into wider society affecting, for example, the behaviour of young athletes well below the elite level. According to Novak (1964), "Since the high school athlete and coach are influenced by the professional and intercollegiate athletes, the amphetamines became popular even in interscholastic athletics" [6]. The factors that accelerated the use of PEDs in the 1950s and early 1960s, nationalism and Cold War rivalry, were intensified in the two subsequent decades but were also augmented by two further powerful factors, government investment in, and the rapid commercialisation of high performance sport. Although some governments, most notably the former German Democratic Republic (GDR) and the former USSR, had for some time treated elite sport as a diplomatic resource, most governments were reluctant to invest public money in sport. However, the willingness of an increasing number of governments from the 1980s to invest public funds in sport, especially elite sport, was due to the combination of (a) USA-USSR rivalry and the recognition of the

diplomatic potential of sporting success, especially at the Olympic Games; (b) the rapid increase in sports broadcasting following the introduction of live satellite transmission of major sports events; and (c) the growing interest in sport as a solution (or at least a palliative) for a number of social ills, such as juvenile delinquency and poor public health. Government interest was also reinforced by the rising commercial value of the sports industry (especially broadcasting, events, leagues and clubs) as a source of employment and profit. In 1912, there were only 20 major international sports events. By 1970, the figure had increased to 350 and by 2005 to 900 [7]. The sports events market was valued at 21,274M USD in 2019 and, despite a severe drop in 2020, was forecast to rise to 31,029m USD by 2024 [8]. Government investment in elite sport has grown in parallel to commercial investment and has been driven by a variety of motives including diplomatic, tourism promotion and nation (re)branding [9]. As the following section will illustrate, the growth in the political and commercial (both corporate and personal) benefits of elite level success has been paralleled by consistent innovation and experimentation in PED use and by the concern of sport organisations and governments to reduce if not eliminate doping in sport. The first list of prohibited substances, compiled by the IOC for use at the 1968 Olympic Games, contained just two classes of substances – stimulants and narcotics [10]. The list has steadily expanded and is now the responsibility of the World Anti-Doping Agency (WADA) and is updated on an annual basis. The list now contains nine groups of PEDs, five that are prohibited at all times (anabolic agents; peptide hormones, growth factors and related substances; beta-2 agonists; hormone and metabolic modulators; and diuretics and masking agents) and four that are prohibited in-competition (stimulants; narcotics cannabinoids; and glucocorticoids). In addition, there are beta-blockers that are prohibited in selected sports, and three doping methods are also prohibited (manipulation of blood and blood compounds; chemical and physical manipulation; and gene and cell doping).

Evolution of PEDs Use

Table 1 provides a summary of some of the major PEDs and methods used in sport and an indication of their current scale of use. What is particularly striking is the relatively short time lag between the development of a particular class of substances and their use in sport.

Stimulants

Stimulants have a long history of exploitation in sport initially based on the use of natural products, but since the middle of the last century based on synthetic stimulants such as amphetamine. Unlike some of the other categories on the WADA Prohibited List, stimulant use developed first outside sport mainly in a military

Table 1 Summary of the most common PEDs and current scale of use

Drug	Approximate date of discovery	First use in sport	Extent of use	Major sports affected	Peak of use	Assessment of current level of use
Stimulants: Amphetamines	1880s (commercial development 1930s)	1940s	Heavy use between the mid-1950s and the late 1980s. Evidence of substantial use by cyclists as an ingredient in the "pot belge"	Cycling, American football, soccer (and many other endurance sports)	Late 1960s to late 1980s	Moderate, due to ease of identification and availability of alternatives
Cocaine	Pre-seventeenth century	Late nineteenth century	Heavy in the late 1960s, particularly among horse racing jockeys and tennis players and then moderate to present day	Many endurance sports and major team sports	Unclear	Moderate
Ephedrine	c1940s	1970s	Heavy use from the mid-1970s to the present	Most endurance sports and many major team sports	Consistent since the 1970s	Heavy
Blood manipulation (methods designed to increase red blood cell count)	Blood doping 1970s	1970s	Moderate	Endurance sports such as long-distance cycling, running, swimming and cross-country skiing	1980s	Moderate, but resurgence in the 2000s as the detection of EPO became easier
Narcotics	Pre-seventeenth century	Late nineteenth century	Heavy between the late 1960s and the present day, but often as recreational drugs as performance-enhancing effect is not clear. However, heroin was used as part of the "pot belge"	Some evidence of use in endurance sports to control pain	Not known	Generally light in elite sport, but still high in some sports/countries, e.g., tramadol abuse

Drug	Approximate date of discovery	First use in sport	Extent of use	Major sports affected	Peak of use	Assessment of current level of use
Anabolic steroids and anabolic agents	1930s	1950s	Heavy between the late 1960s and the late 1980s	Most Olympic sports and many major team sports	Consistent since the 1980s	Heavy
Peptide hormones: For example, EPO	rEPO 1987	Late 1980s	Light in late 1980s but heavily used from the 1990s	Endurance sports	Perhaps 2010s	Heavy to moderate
Human growth hormone	Mid-1980s	Late 1980s	Moderate	Body-building and a similar range of sports that attract anabolic steroid users	Yet to be reached	Moderate, but rising
Diuretics and other masking agents	Synthetic diuretics 1960s	1970s?	Moderate to heavy in the early 1970s	Weight-related sports, but all sports when used as a masking agent	Mid-1970s	Moderate use in weight-related sports or as a part of a dietary supplement, despite the relative ease of identification
Beta-blockers	1960s	1970s	Moderate use in small number of sports	Shooting, archery and snooker	Late 1980s	Light
Genetic manipulation	1970s	No confirmed cases	Rumours and speculation, but no evidence of use	Potential to affect all sports		None to negligible
Novel psychoactive substances	A fragmented history, but came to the notice of drug agencies in the late 1990s	1990s	Moderate, but difficult to determine accurately	Potential use in all sports	Probably not yet reached	Moderate to heavy

context and, in the 1960s and 1970s, as a recreational drug among adolescents. As mentioned previously the use of amphetamines and related stimulants was first identified in endurance events especially road cycling but also in long-distance running and swimming as well as some team sports such as football in the 1950s and 1960s. Since then a large number of stimulants that mimic the effects of amphetamine have been developed for therapeutic use and have subsequently been used by athletes. One of the most notable is ephedrine, a substance that was, at one time, common in over-the-counter cold remedies. The use of the drug in sport came to public attention in 1972 when the American swimmer Rick DeMont tested positive for ephedrine at the Munich Olympic Games. Since then ephedrine has been regularly detected in doping controls although other stimulants such as methylphenidate, cocaine, and heptaminol have been identified more frequently in anti-doping controls [11]. Stimulants remain a major concern for anti-doping organisations. Between 2014 and 2017, stimulant use was identified by WADA as a regular occurrence in most major sports including cycling, athletics, aquatics, weightlifting and boxing [12] and in WADA's 2018 anti-doping report stimulants was the second most commonly identified class of drugs [11].

Anabolic Agents

One of the first clinical uses of this class of drugs was to aid the recovery of patients suffering from starvation in the 1930s. Later during the Second World War, anabolic steroids were used in the German army to increase the aggressiveness and strength of soldiers. Reports of the use of anabolic steroids in sport began to emerge in the early 1950s. At the 1952 Helsinki Olympic Games, rumours circulated that members of the Soviet Union team had used anabolic steroids as part of their training preparations and that this partly explained the success of the team in winning 71 medals just five short of the USA total. Rather than these rumours leading to attempts to prevent further use, they fuelled the rivalry between the USA and the Soviet Union. The spread of anabolic steroid use in the USA was facilitated by the willingness of some doctors to supply PEDs to US athletes. As Goldman and Klatz noted, "When steroids first came on the scene there were many physicians, including the father of anabolic steroids, Dr. John Ziegler, who cautiously embraced them, and willingly prescribed them to athletes for whom they were responsible … Patriotism was a factor as well. The feeling of these doctors was that if they could in any way help an American athlete bring home the gold, they had somehow struck a blow for freedom" [13]. Further evidence of the use of anabolic steroids by Soviet athletes emerged at the 1956 Olympic Games where the use of the drug was so great that, according to Voy (1991), some Soviet athletes had to be catheterised in order to pass urine due to the enlargement of the prostate gland [14]. Ziegler began to experiment with synthetic testosterone to test their performance-enhancing potential at about the same time that the Ciba pharmaceutical company was developing steroids for clinical use with burn victims. The outcome of the development was the

steroid trade-named Dianabol. Ziegler persuaded three American weightlifters to experiment with Dianabol with the result that "all three experienced significant improvements in both strength and muscle mass. Following this success, the use of Dianabol spread rapidly among U.S. lifters and, from there, to other sports" [15].

The use of steroids was initially confined to the power sports such as weightlifting and throwing events but soon spread to other sports such as swimming. The increase in the use of this class of drugs was partly the result of the recognition that not only could the drugs be effective in adding muscle mass but that they were also effective in enabling athletes to train longer and recover faster from intensive periods of training. By the 1970s, the use of anabolic steroids was widespread, and it was not until a reliable test had been developed to detect the drugs that use began to slow. Tests were conducted at the Montreal Olympic Games in 1976, and eight athletes were disqualified for the use of anabolic steroids. However, rather than the development of a reliable test marking a decline in steroid use, it merely marked the first phase in an ongoing competition between steroid users and anti-doping organisations. Doping rule violations involving steroids continued into the 1980s. At the 1983 Pan-American Games many athletes withdrew when they were made aware of the likelihood of being tested for steroids, and 19 athletes tested positive for PEDs, some of which were steroids. However, it was later in the decade that the scale of steroid use began to become apparent. In 1987, 34 people, including the British Olympian David Jenkins, were indicted by the US Drug Enforcement Administration for smuggling steroids worth around $100m from Mexico to the USA. The following year Ben Johnson tested positive for steroids after winning the 100 m final at the Seoul Olympics. Evidence of the widespread use of steroids in high performance sport and increasingly among non-elite athletes and indeed non-athletes continued to emerge during the 1980s and 1990s. The enquiry into doping in sport in Australia [16] reported that around 70% of all positive doping controls in IOC-accredited laboratories were for steroids. The popularity of steroids among PED users continued into the twenty-first century with the WADA report [17] for PED use in 2010 noting that just under 81% of all reported findings were for steroids. Although the 2018 WADA testing figures reported that steroid use had dropped to 44% of all reported findings, this class of PEDs was still by far the most commonly found [11]. While the continued popularity of steroids among elite athletes is a substantial challenge for anti-doping authorities, the spread of steroid use beyond the confines of elite sport has emerged as a significant contemporary public health concern. Two developments in the spread of steroids are of particular concern: the spread among school-age young people and among gym users. According to Dandoy and Gereige (2012), the US National Youth Risk Behavior System which surveys over 16,000 9th to 12th grade students reported that the incidence of steroid use had risen from 2.7% in 1991 to 6.1% in 2003 before declining to 3.3% in 2009 [18]. The rise in steroid use was accompanied by a "sharp decline" in the perception of risk associated with steroid use. Further evidence came from the National Institute on Drug Abuse which estimated that over 500,000 8th and 10th grade students, predominantly those involved in sports including American football, baseball and basketball, were using steroids (NIDA 2004). In a later study, NIDA reported that steroid

use among 8th and 10th grade high school students had peaked around 2000 and had "generally declined" although use among 12th grade students "increased from 2011 to 2015" before declining from 2015 to 2016 and then stabilising [19]. There are relatively few studies of adolescent steroid use outside the USA, but those that exist present a broadly similar picture. Nilsson et al. (2001) found that 3.6% of 16-year-old males in a survey of 5827 16- and 17-year-olds in Sweden admitted to using steroids (2.8% for 17-year-olds) [20]. A study in Poland reported that in their survey of 1175 male and female students, 9.38% of males and 2.08% of females reported having used steroids. The authors reported that the main motives for steroid use "were connected with shaping their bodies in a manner allowing realisation of cultural ideals of bodyshape" [21]. Broadly similar results were reported from a range of studies across Europe indicating a significant public health problem among adolescent males especially among those involved in youth sport (e.g., [22, 23]). Overlapping with the prevalence of steroid use among adolescents is the increasing use among gym users. Numerous studies have indicated that steroid use is evident among gym users although precise figures regarding usage are difficult to obtain. Stubbe et al. (2014) reported usage of steroids by 1% of gym users (with 0.8% reporting using prohormone and 1.1% using growth hormone or insulin) although the most frequently used PEDs were stimulants (4.8%) to help reduce weight [24]. McVeigh and Begley (2017) reported a substantial increase in steroid users (not all of whom were necessarily gym users) accessing local needle and syringe programmes in two counties in north-west England (553 clients in 1995 and 2446 in 2015) [25]. Christiansen (2015) summarised a number of studies from Nordic countries indicating a prevalence rate for steroid use of 3.8% (Sweden) and 5% (Denmark) [26]. He also noted that "for users in the gym environment most evidence suggests that use … is restricted to a limited period of the individual's life … from late teens to early thirties" [26]. Unlike the pattern of use of stimulants where use appeared to develop in elite sport and broader society in parallel, the spread of steroid use to junior athletes and to gyms appeared to have followed the demonstration effect of use by elite athletes.

Peptide Hormones: Human Growth Hormone

Human growth hormone (hGH) is one of the newer PEDs in sport and was developed in the mid-1970s as a replacement for natural endogenous growth hormone. By the late 1980s, there were reports of athletes using human growth hormone often at many times the recommended therapeutic levels even though there had been no peer-reviewed papers providing evidence of its performance-enhancing effect. Despite the lack of evidence, Sonksen et al. (2016) noted that "so great was the demand for GH that stocks of GH in pharmacies and warehouses and even trucks on the road were targeted" [27]. One of the earliest verified cases of use of human growth hormone was in evidence given to the Dubin Inquiry following the Ben Johnson scandal in 1988. The sprinter Angella Issajenko admitted using hGH along

with other drugs. The report of the Inquiry noted that "Notwithstanding the strict control of growth hormone there was evidence of increased use by other sprinters, bodybuilders, weightlifters and intercollegiate football players whose sole source of supply has been the black market" [28]. Human growth hormones tend to be used by athletes seeking similar advantages as expected from steroids, but they are more attractive to those seeking to improve musculature rather than simply enhance muscle strength. However, the discovery of 13 vials of hGH in the luggage of a member of the China swimming team in Perth in 1998 suggests that the drug is also valued by those athletes in explosive and endurance events. The IOC identified GH use as a concern in the early 1990s, but it was not until the London 2012 Olympic Games that testing for GH took place. As Sonksen et al. (2016) note, "Knowledge about the misuse of GH is unreliable as our intelligence is largely based on hearsay and anecdotes as testing for GH has been limited but it appears to be particularly popular in sprint and power sports usually in combination with anabolic steroids" [27]. The latest WADA testing figures [11] indicate the continuing use of peptide hormones, growth factors, and related substances with them accounting for 3% of adverse analytical findings and 31% of atypical findings. WADA's report on 2018 testing figures expressed concern about the use of GH and encouraged an 18% increase in the number of tests between 2017 and 2018 [11].

Diuretics

Diuretics are drugs that are used to increase the rate of urine formation [29]. The modern suite of diuretics dates from the mid-1950s and has been used in sport for three main purposes: (a) to achieve rapid weight loss in weight-graded sports such as boxing and wrestling; (b) to flush other drugs out of the system; and (c) to counteract the fluid-retention properties of steroids. The last purpose is attractive to bodybuilders who use diuretics to achieve a more sharply defined musculature. While it can be assumed that the use of diuretics by elite athletes took place in the 1960s and 1970s, it was not until the 1980s that evidence of use by athletes began to accumulate. One of the earliest examples of the use of diuretics involved a Canadian athlete at the 1983 Caracas Pan-American Games, but as diuretics were not on the IOC list of prohibited substances, no anti-doping rule had been broken. Diuretics were added to the IOC list in 1985, and since then there have been regular reports of violations involving this class of drugs each year. Examples of anti-doping violations involving diuretics include the British judo athlete who tested positive for the diuretic furosemide in 1988, the cyclist Pedro Delgado who tested positive in the same year and Veronica Campbell-Brown (winner of three Olympic gold medals) who tested positive in 2013. Data from WADA indicates a steady rise in the proportion of adverse analytical findings that involve diuretics: in 2003, there were 142 occurrences (5.2% of all positives); in 2008, 436 occurrences (7.9%); and in 2018, 589 occurrences (14%). Outside of Olympic sports, use of diuretics is also evident among bodybuilders although use is far behind that of steroids (e.g., [24, 30, 31]).

Beta-Blockers

Beta-blockers are used to treat a range of medical conditions such as migraine and angina. In sport they are used to reduce anxiety levels, steady breathing and reduce heart beat frequency and muscle tremor. While they are of little value in most sports, they can be beneficial in those that require a steady hand such as shooting, archery, darts and snooker. Beta-blockers came to the notice of sports federations in the 1980s. Evidence of the use of beta-blockers was found among competitors in shooting events and modern pentathlon in the 1984 Olympic Games, and later in the 1980s, a number of snooker players were reported to have been using this class of drugs. Beta-blockers were not prohibited at the time of the Los Angeles Olympic Games although team doctors were obliged to notify the IOC of any team members taking the drug. The number of notifications, sometimes whole teams, alarmed the IOC who added beta-blockers to the prohibited list in 1985. Current usage of beta-blockers appears to be low [11] although there are occasional high-profile cases at Olympic Games such as the positive test for propranolol in the sample of the North Korean shooter Kim Jong-Su at the 2008 Games in Beijing.

Genetic Manipulation

The history of doping in sport provides ample evidence of the willingness of athletes to use drugs before clinical trials have been completed, to use drugs specifically designed for use in a veterinary context and to use drugs in amounts that far exceed therapeutic limits. It is, therefore, highly likely that this propensity for risk-taking will manifest itself in relation to genetic manipulation. An early warning of the interest from athletes in advances in gene therapies came when an email from the coach Thomas Springstein was read out in court in 2006 in which he enquired about the drug Repoxygen, a virus-based drug carrying the human EPO gene which would have similar blood-boosting properties to rEPO. WADA had added gene doping to its prohibited list in 2003, and research continues to identify detection methods. At present there are no verified cases of gene doping, but experimentation by athletes is inevitable. Lopez et al. (2020) summarise the potential candidate genes associated with sport performance and note that many of the current gene therapy trials are addressing clinical problems that have a clear cross over to doping in sport and include those associated with oxygen delivery, pain tolerance and muscle growth/repair [32]. The threat to clean sport from gene doping is substantial and is a major challenge for anti-doping authorities.

Novel Psychoactive Substances

Novel psychoactive substances (NPS) may be "novel" in a variety of ways. NPS may refer to "something newly created, an old drug that has come back into fashion, or a known NPS molecule being used in an innovative or unusual way" [33]. From 2004 to 2017, between 700 and 800 examples of NPS were identified by European and international drug agencies with the most common examples being "synthetic cannabimimetics, synthetic opioids, phenethylamines, designer benzodiazepines, and prescribed drugs" [33]. As Mazzoni et al. (2017) observed, "Among the doping substances, the most preoccupying is the increased supply of counterfeit and designer drugs, including NPS. NPS have a long history of abuse in sport" [34]. Most NPS fall within the categories of stimulants, narcotics and cannabinoids on the WADA list of prohibited substances and practices. The growth in the availability of NPS is proving to be a particularly daunting challenge for WADA. First, as Mazzoni et al. (2017) note, "the identification of prohibited substances… requires the previous knowledge of the chemical structure of the substance and its mass spectrum none of which are known for NPS recently introduced in the market" [34]. The acquisition of knowledge of the chemical structure of NPS relies on NPS being sent to WADA or its network of laboratories or the direct purchase of NPS from the Internet. Second, "the risk of inadvertent doping with supplements is high because it is common that NPS are not named on the labels or sometimes they are referred to with a fictional name … or by a purposely wrong chemical name" [34]. Third, detection of some NPS, particularly synthetic cannabinoids, is made more difficult as they appear to be unrelated to their natural counterparts. In addition to the problems of detection, there are serious challenges in limiting supply. It is estimated that 80% of the raw materials for the clandestine manufacture of counterfeit and illegal drugs abused in sport come from China. WADA is working closely with the Chinese authorities to reduce supply, but it remains to be seen how effective the Chinese efforts will prove to be.

Conclusion

Prior to the establishment of WADA, the fragmented and under-funded nature of anti-doping action meant that anti-doping authorities were always some way behind drug users both scientifically and organisationally. There was often a long delay between a PED being identified in sport and its incorporation into the IOC prohibited list and the development of a reliable test that would withstand legal challenge. The establishment of WADA has harmonised anti-doping regulations and provided valuable coordination of anti-doping research. Equally importantly the Agency has built links with the pharmaceutical industry, customs and excise departments and law enforcement agencies and established a secure whistleblowing procedure and an internal investigations capacity. These positive developments notwithstanding

the Agency and sport organisations still face considerable challenges as innovation in the development, modification and administration of PEDs continues. In addition, the lack of consistent support for anti-doping from some governments and the ambivalent attitude of some international federations continue to pose problems for the implementation of an effective global response to the problem.

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