

·Review·

Androgenic-anabolic steroids and the Olympic Games

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Abstract

Androgenic-anabolic steroids (AAS) have been misused by athletes at the Olympic Games, both before and after they were prohibited in sport in 1974. Systematic doping with AAS occurred in the German Democratic Republic (GDR) from 1965 to 1989 which assisted that country to win many medals at Olympic Games, especially in female events. Currently, AAS are the most frequent category of prohibited substances detected in the urine of athletes both globally and at the last two Summer Olympic Games. Scientific confirmation that AAS are effective in enhancing sports performance was difficult because ethical approval was difficult for research involving male subjects taking massive doses of androgens as some athletes and bodybuilders did. Methods to detect AAS have evolved gradually over the past three decades and currently, despite an impressive array of sophisticated analytical equipment and methods, anti-doping authorities and analytical scientists continue to face challenges as have occurred from the use by athletes of designer AAS during the past few years. The future development and use of selective androgen receptor modulators (SARMs) can be anticipated to pose problems in the years ahead. Endocrinologists should be aware that on occasions, replacement testosterone (T) therapy may be authorized in sport as a therapeutic use exemption (TUE) and these circumstances are discussed. (*Asian J Androl*, 2008 May; 10: 384–390)

Keywords: doping; androgenic-anabolic steroids; history; Olympic Games; detection; designer steroids; therapeutic use exemption

1 Introduction

Since the ancient Olympic Games in Greece, athletes have endeavoured to enhance their performance through artificial means. During the last five decades, androgenic-anabolic steroids (AAS) have been one of the most commonly used and effective groups of drugs that have assisted athletes to achieve improved sports performance. Yet AAS were not prohibited in sport until 1974. Unlike some other ergogenic aids, AAS provide greater benefit if administered during training than immediately prior to competition. Anti-doping authorities have continually attempted to reduce and if possible eradi-

cate cheating by AAS misuse. This review will examine the history of doping by athletes with AAS, especially testosterone (T), with an emphasis on the Olympic Games. It will discuss the methods used to detect such misuse but observe that throughout, this has been a constant attempt to catch up to scientists, coaches and others who unethically aid athletes to cheat. Finally, the permitted use of AAS, predominately T, to treat genuine medical conditions experienced by athletes will be discussed.

2 Early history of T use by athletes at the Olympic Games

In 1935, T was isolated, synthesized, its anabolic properties identified by several groups of researchers and a commercial preparation became available for androgen deficient males. Quoted in most accounts of the history of doping in sports is that a US physician Dr John Ziegler travelled to Vienna with the US team for the 1954 World Weightlifting Championship and is alleged to have been informed by a Russian official that the Soviet weightlifters were taking T. On his return, Dr Ziegler began to administer T to weightlifters at his gymnasium in Pennsylv-

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Ivania. In 1958, when Ciba released methandrostenolone (methandienone, Dianabol®), Dr Ziegler switched to this preparation. Following publication in the non scientific press of his experiments and the success of power athletes after taking methandienone, the use of AAS commenced to be used in a wide range of sports [1].

Although the use of AAS may have occurred as early as Olympic Games in the 1950s, it seems clear that some athletes did administer AAS at the Games during the 1960s (Rome 1960, Tokyo 1964 and Mexico City 1968) and such use was more prevalent at the 1972 Munich Olympics [2, 3].

3 Systematic doping with AAS at the Olympic Games

Because the results of doping with AAS have included enhanced sporting success, a number of countries have failed to act when their athletes have tested positive to prohibited drugs while others have turned a blind eye to organized doping that was occurring amongst some of their athletes. However, no country has ever embraced a national system of scientific doping perpetrated by doctors, sports scientists and coaches and masterminded by the state as did East Germany (the misnamed German Democratic Republic, GDR) between 1965 and 1989. The unification of the two Germanys that commenced in late 1989 has unearthed some documents that had not been shredded and these have detailed the extent of these doping practices. Evidence given by former athletes during trials in Germany of doctors and officials who oversaw and implemented this program revealed the extent of the acute and permanent side-effects of the administration of AAS on them and even of the late consequences on their children [4, 5].

GDR was a relatively obscure Soviet satellite of with a population of 17 million that resolved to achieve international recognition and respect through success in sport. Backed by a talent identification program that was well ahead of its time, sports schools and clubs staffed by sports medicine specialists, sport scientists and well qualified coaches, all financially supported by the state and offering significant rewards in money and kind to its successful athletes and their families, GDR was likely to have become a major force in international sport even without resorting to systematic doping.

After the development of chlor-substituted derivative of methandrostenolone (Oral-Turbinabol®) by a state-owned pharmaceutical company in 1965, GDR commenced to administer it predominately to female athletes in preparation for the 1968 Olympic Games. Known as *Unterstützende Mittel* (UM or supporting means), oral Turbinabol® was supplemented by mestanolone (STS 646), briefly by injected nandrolone esters (ceased because a female shot putter tested positive) and finally T by injection [6]. UM was provided mostly to female ath-

letes with impressive improvements in performance. Additional evidence to confirm the success of this national doping with AAS can be obtained by comparing the results of East Germany (EG) and West Germany (WG). Prior to the commencement of the UM program, in the three Olympic Games 1956–1964, EG won 45 Olympic medals compared to 81 by WG. In 1968, soon after the UM program commenced, EG with 25 medals closed on WG's 26. In the next three Games in which both competed (boycotts eliminating WG from 1980 Moscow and EG from 1984 Los Angeles Olympics), 1972, 1976 and 1988, EG won 258 medals compared with 119 by WG [7].

4 Why athletes dope with AAS

The scientific literature was years behind the “underground press” in acknowledging that AAS improved sports performance. The underground press was begun by Dan Duchaine from Los Angeles who for many years published the *Underground Steroid Handbook*, a combination of knowledge acquired from reading scientific sources but principally from personal knowledge and experience with bodybuilders and athletes who followed his AAS regimes [8, 9]. Two scientists, Hatfield [10] and Di Pasquale [11] quickly followed in the promotion of AAS, especially for bodybuilders. Primarily because uncontrolled studies had administered only physiological doses of T [12], it was not until 1996 in a double blind controlled study, that Bhasin and colleagues [13] in Los Angeles administered suprphysiological doses of T (600 mg of T enanthate per week for 10 weeks) and demonstrated increased muscle size and strength, even without exercise. Greater gains in arm and leg strength were achieved by subjects who were administered T and exercised. The same researchers [14] reported that the administration of T to young and older eugonadal males increased lean body mass and reduced fat mass, changes being dose but not age dependent.

Although unconfirmed by scientific evidence, users of AAS have repeatedly acknowledged that AAS result in an ability to train and compete harder and more aggressively and to recover more quickly from hard training sessions and competitions. The scientists and coaches of the GDR were aware 30 years before Bhasin as has been disclosed from information obtained after the unification of Germany. It was documented that treatment with AAS for four years, coupled with scientific training methods could improve shot put distance in men by 2.5–4 m and in women by 4.5–5 m; women were 4–5 s faster over 400 m and 7–10 s faster over 800 m [6]. Evidence of this exists today because no female athlete has come within half a second of the longest standing track and field record 400 m set in 1985 by a GDR female athlete treated with UM [15]. One crucial aspect that impaired

the scientific examination of the effects of AAS was that athletes used massive doses of not one but several different AAS, taken concurrently. Often the consequences were huge gains in strength and power and many side-effects. Scientists could never obtain ethical approval to conduct research involving such polypharmacy and suprathreshold doses. "Stacking" (taking two or more AAS concurrently) and "cycling" (commonly a 6–10-week cycle followed by a drug-free period of a similar length to reduce side-effects and tolerance) have been practiced for many years by bodybuilders not subjected to drug testing and having little respect for either their bodies or the side-effects [8, 9]. In a review of 500 anonymous AAS users, 78% of whom were non competitive bodybuilders or non athletes, almost 60% reported administering at least 1 000 mg of T or its equivalent a week, with 25% admitting the concomitant use of human growth hormone (hGH) and insulin for their anabolic effects. Not surprisingly, 99% reported side-effects from AAS use [16].

5 Detection of T misuse by athletes

In 1967, the International Olympic Committee (IOC) established a Medical Commission (IOC-MC) whose primary role was to fight the misuse of drugs by Olympic athletes. Between 1967 and 2003, the IOC-MC compiled a List of Prohibited Substances and Prohibited Methods for the Olympic Games. A majority of International Sport Federations (IFs) adhered to this list although some IFs had their own lists. The accreditation of Sports Anti-Doping Laboratories was commenced by the International Association of Athletics Federations (IAAF) in the mid 1970s with the responsibility ceded to the IOC-MC in 1983 by mutual agreement. The World Anti-Doping Agency (WADA) assumed both these roles in 2004.

Token testing was undertaken at the 1968 Games but it was not until the Munich Olympic Games in 1972 that a major drug testing program was introduced with more than 2 000 tests undertaken, albeit only for stimulants and narcotics. The absence of any analytical test to identify AAS is the presumed reason why the IOC delayed in prohibiting them in sport. With hindsight and subsequently, the IOC did prohibit other doping agents without any possibility of detecting their administration, e.g. blood doping in 1985, hGH in 1989, erythropoietin in 1990, this was an error.

For many years, accredited laboratories have identified more adverse analytical findings in the category of anabolic agents than in any other prohibited class. In 2006, the 33 WADA accredited laboratories in 29 countries reported 1 966 (45.4%) of the 4 332 adverse analytical findings were anabolic agents. Of these, 57.2% were T, 12.1% nandrolone, 11.3% stanozolol and 6.4% methandienone [18]. However, it must be stressed that these numbers do not represent sanctioned anti-doping rule violations as some may have been athletes who had a therapeutic use exemption for T and others could have been a consequence of additional investigations conducted after an elevated testosterone/epitestosterone (T/E) ratio was identified.

6 AAS detection by radio-immunoassays

In 1974, after Brooks and colleagues in London [19] had developed radio-immunoassays (RIA) that could detect some AAS, the IOC prohibited AAS with the first positives at the 1976 Montreal Games. A total of eight athletes were disqualified for use of methandienone, seven weightlifters and one athlete in a field event. No positive tests were announced at the boycotted 1980 Games in Moscow. Having closely observed the physique of the Eastern Block athletes, especially females in power events,

Table 1. Accessed from the internet, this 8-week cycle, recommended for an experienced male steroid user of 110 kg involved "stacking" three AAS and adjusting the dosage for body weight by a factor of 10% per 10 kg of body weight. Nolvadex® (tamoxifen) was recommended for those with a history of gynaecomastia. Other recommended cycles included Pregnyl® (hCG) 5 000 IU a week in last 2–3 weeks of the cycle or Clomid® (clomiphene) 50 mg daily for the last two weeks of the cycle to re-stimulate the suppressed endogenous testosterone [17].

Week	Anadrol®	Sustanon®	Deca®	Dianabol®	Primobolan®
	Oxymetholone (mg/day)	Testosterone esters (mg/week)	Nandrolone decanoate (mg/week)	Methandrostenolone (mg/day)	Methenolone (mg/week)
1	50	750	100	–	–
2	50	500	100	–	–
3	50	500	300	–	–
4	50	250	400	–	–
5	50	–	400	50	100
6	–	–	300	50	200
7	–	–	200	50	300
8	–	–	100	30	300

the author was sceptical especially when it was stated that the absence of positives tests was alleged because the RIA test was performed. Post Games, the unused B samples were transported to be analysed anonymously by gas chromatography and mass spectrometry (GC/MS) at the IAAF accredited Laboratory in Cologne, Germany. Although no information on how many of these samples contained doping agents was ever published, a subsequent PhD thesis reported 7.1% of all females urines at the Moscow Games had a T/E ratio > 6 [20].

7 AAS detection by GS/MS, HRMS and the T/E ratio

In 1982, having analysed 2 700 urines including the B samples from Moscow 1980, Donike *et al.* [21] identified that the ratio of the concentration of urinary T to its 17α epimer E (the T/E ratio) was around unity. He proposed that if the T/E ratio exceeded 3, this was indicative of misuse of T but was persuaded to increase this to 6 and this became valid in 1983.

Unknown until after the demise of the GDR in 1989, the head of the GDR Doping Laboratory in Kreischa, Germany, Clausnitzer possessed greater knowledge of the T/E ratio than anybody including his ethical West German counterpart Donike in Cologne, Germany. Within one year of the introduction of the T/E ratio to detect doping with T, Clausnitzer had researched the subject in his large pool of elite athletes being systematically doped and undertook pre-testing of his athletes before they competed internationally. E was available in GDR in 1983 and was administered to athletes to reduce their T/E ratios to less than 6 [6]. The most ironic and frustrating aspect for the author was that Clausnitzer was a member of the IOC-MC from 1981 to 1989.

The 1984 Olympic Games were the first where GS/MS was used to detect and identify AAS. A cross country skier at the Winter Olympic Games in Sarajevo was positive for methandienone and nine athletes were disqualified for AAS use at the Summer Games in Los Angeles, five for nandrolone and two for both methenolone and T [22]. The most bizarre was the middle distance runner, who had also blood doped with autologous blood (blood doping was not prohibited until 1985) and had been taking methenolone when his blood was withdrawn. After being stored for several weeks, his blood was re-infused pre race and the methenolone was administered. Two athletes were noted to have a T/E ratio in excess of 6 and were disqualified. One, a hammer thrower was stated to have a very high urinary T concentration. The other, a Japanese volleyball player, had a urinary T concentration of 70, a T/E of 10 and thus low levels of E. As anabolic steroids would be unlikely to be misused by a volleyball player, it was questioned if this athlete had a naturally occurring elevation

of his T/E ratio. Further investigations were performed in Japan and revealed that this athlete did have a naturally elevated T/E ratio [23]. Despite this result and the methods the GDR scientists employed to ensure athletes did not compete with a T/E ratio greater than 6, the concept of the T/E ratio did present a threat to the unrestrained misuse of T by athletes.

At the 1988 Winter Olympics in Calgary, an ice hockey player with a T/E > 8.0 was disqualified for T misuse [24]. In contrast, at the Seoul Olympics in 1988, a US basketball player had a T/E ratio of 7.1 but was exonerated because three previous tests performed in USA during 1988 had all demonstrated a T/E ratio of between 5.4 and 5.8. The co-efficient of variation was deemed to be low (10%) and the sample was declared negative. Seoul 1988 was notable for the disqualification of the winner of the 100 m final because he tested positive for the AAS, stanozolol as did two other athletes. Barcelona 1992 resulted in two power athletes being sanctioned after they tested positive to clenbuterol, a beta 2 agonist with anabolic properties and highly recommended for bodybuilders [9]. It was not until 1992 that the IOC decided that all urine samples with a T/E between 6 and 10 must be investigated, either by reviewing previous tests or by undertaking three unannounced tests over a three-month period before declaring the athlete positive for doping with T. Any sample with a T/E ratio > 10 was automatically declared positive. Two years later, the IOC reviewed this clause and decided that all urines with a T/E greater than 6 should be investigated before being declared positive. High resolution mass spectrometry (HRMS) was introduced for the 1996 Atlanta Olympic Games but no AAS were detected in any athlete's urine.

Although there has been no general direction made for Laboratories to correct concentrations of Prohibited Substances for specific gravity (SG), since 2004 WADA has advised laboratories to correct urinary concentrations of endogenous steroids to a SG of 1020 [25]. Corrected concentrations of T > 200 ng/mL are suggestive of the administration of T. The administration of E occurred initially in GDR to normalise T/E ratios and in 2004, WADA stated that corrected urinary concentrations of E > 200 ng/mL are suspicious of the administration of E [26]. Complicating this issue is that E production is often reduced by the administration of AAS including T. Thus, consistently stable concentrations of E are not suggestive of the use of exogenous T.

In 2005, WADA lowered the T/E cut-off from 6 to 4 for two main reasons. Firstly, some authorities considered that athletes were doping with low dose T, especially patches and gels and remaining below the T/E cut-off of 6 [27]. Secondly, many East Asian athletes have a normal T/E ratio significantly below 1 and a 6–10-fold increase in the ratio may not exceed 6 [28, 29]. However,

this has not produced any increase in athletes being identified as doping with T. Rather, it has resulted in large increases in work and costs for anti-doping agencies as more and more athletes require unannounced follow-up tests. Currently WADA employs a co-efficient of variation of 30% for males and 60% for females when assessing whether past or subsequent tests confirm that the athlete has a normally elevated T/E ratio. The co-efficient of variation is not a strictly enforced and laboratories can use discretion when reviewing the overall steroid profiles. The commonest reason for a naturally elevated T/E ratio is low excretion of E, the inactive epimer of T. Other less common causes are androgen secreting tumours, predominately in females and enzyme deficiencies.

Although the rationale for reducing the T/E cut-off from 6 to 4 appeared sound, history had already demonstrated that it was a questionable decision. As early as the 1988 Winter Olympic Games in Calgary, the laboratory reported 17 athletes (15 males and two females) had T/E ratios between 4 and 6 [24]. In 1996, the accredited Laboratory in Stockholm investigated 28 of 8 946 urines that had a T/E > 6 and conclude that only one with a T/E of 10.5 and a CV of 126% could be confirmed as doping with T [30]. It is possible that some of these athletes in Calgary and in Sweden may have been low dosing with T because GC-combustion-isotope ratio mass spectrometry (IRMS) [31] was not yet available.

Since January 2005 when WADA reduced the T/E cut-off to 4, in a review of Australian athletes who have had to be further examined because of their T/E ratio was between 4 and 6, the author has identified that the annual numbers of cases necessitating further investigation have increased more than three-fold and not one athlete whose T/E ratio was between 4 and 6 has been identified as having used exogenous T, with IRMS performed in every instance.

8 Detection of AAS by other methods

Because the administration of T inhibits LH production, in 1979, Brooks and colleagues [32] recommended the ratio of urinary T to LH as a valuable index to identify doping with T and re-examined this premise a decade later [33]. Another group demonstrated that after an injection of T, the T/LH ratio remains significantly elevated longer than the T/E ratio [34]. The negative aspect is that after more than 25 years, there is no standardized urinary immunoassay or methodology to measure urinary LH and this has contributed to the T/LH ratio not becoming globally accepted as the gold standard index although it does remain an ancillary indicator suggestive of exogenous T administration [27].

9 Detection of AAS by GC-combustion-IRMS

Synthetic androgens, derived by semisynthesis from plant origin, have less ^{13}C than their endogenously produced counterparts and thus allow a potential differentiation of the ^{13}C content between endogenous steroid metabolites and their synthetically derived analogues. The method is by GC with combustion to CO_2 and mass spectrometric analysis of the gas in a mass spectrometer (gas chromatography-combustion-isotope ratio mass spectrometry [IRMS]). The aim is to compare the urinary $^{13}\text{C}/^{12}\text{C}$ ratio with reference steroids in the sample unaffected by exogenous administration. Where any parameter in the steroid profile indicates the need for further investigation, most commonly T because of a T/E ratio > 4, the $^{13}\text{C}/^{12}\text{C}$ value expressed in δ units per mL ($\text{d}^0/_{100}$) of that steroid or its metabolites is measured [35]. If the $^{13}\text{C}/^{12}\text{C}$ value differs by 3 δ units or more from the urinary reference steroid chosen, this is considered consistent with the exogenous administration of that AAS [26]. IRMS can detect the administration of E [36].

IRMS was accepted by the IOC in 1999 as an approved analytical method and used by the Laboratory at the Olympic Games in Sydney 2000. However, IRMS was not required to identify any of the six AAS positive at these Games; four nandrolone, three of which were low level (< 7 ng/mL) and likely to have been ingested inadvertently in supplements and two stanozolol. All six athletes were disqualified. In Salt Lake City 2002, two athletes were positive for nandrolone. The first Olympic competitor disqualified as a result of IRMS for misuse of T was a Greek wrestler at the Athens Olympic Games 2004. At the 2004 Games, five other athletes tested positive for AAS; stanozolol three, oxandrolone one and metabolites of methyltestosterone one. Two other athletes were disqualified for using clenbuterol.

10 Designer AAS

In recent years, three designer anabolic agents that have never been marketed have been identified. The first was discovered in 2002 by Catlin, head of the UCLA Analytical Laboratory [37], who detected a potent 19-nor anabolic steroid norbolethone the urine of a female cyclist. In 2003, Catlin received a used syringe containing a residual substance tetrahydrogestrinone (THG), which he identified, synthesized by hydrogenation of gestrinone and a developed specific method of detection [38]. THG has been demonstrated to be a highly potent androgen and progestin [39] and several athletes have been sanctioned for its use. As some of these athletes participated at the Sydney Olympic Games, the obvious question was whether THG was used by athletes at the 2000 Games? In 2007, the most successful female track athlete who won five medals including three gold at the

Sydney Olympic Games, admitted that she had taken designer steroids since 1999 and returned her medals. Also in 2003, Canadian custom authorities at the US-Canadian border seized a quantity of steroids which were identified as desoxy-methyl-testosterone (DMT). Further investigation by Catlin and colleagues [40] and in Germany [41] both of whom termed the substance “madol”, demonstrated DMT to be a potent androgen receptor agonist with anabolic activity and could be detected in urine.

11 The future selective androgen receptor modulators (SARMs)

The concept of SARMs, first introduced in 1999 [42] has progressed to early phase clinical trials in the development of non-steroidal selective androgen receptor agonists. These appear to have the likelihood of inducing anabolic effects on muscle and bone with minor androgenic effects. It is these androgenic side-effects that constitute a major disadvantage of AAS misuse [43]. Thus SARMs have the potential to be highly effective doping agents in the future and not surprisingly, WADA has prohibited SARMs in sport from 1 January 2008 [44].

12 Beijing 2008

The Beijing Doping Laboratory for the 2008 Olympic Games will have the most sophisticated state of the art analytical equipment which will be at the disposal of the most experienced team of chemists ever assembled at an Olympic Games. Three thousand five hundred blood and urine samples will be collected and analysed in the month from the opening of the Olympic Village on 27 July 2008. This is an increase of 22% of tests from Athens 2004. The IOC and the Beijing Organising Committee are making strenuous efforts to limit doping with AAS and other substances at the 2008 Olympic Games.

13 Permitted administration of AAS to athletes

After glucocorticosteroids, diuretics and beta blockers were prohibited in sport by the IOC in 1985, some athletes with medical conditions became significantly disadvantaged. In the late 1980s, two athletes were given permission to administer T and participate in national competitions only. One in Sweden had had both testes removed for malignancies and the other an Australian had neonatal torsions of both testes. It was not until 1992 that the IOC agreed to a policy that allowed the permitted use of prohibited substances for genuine medical conditions. Subsequently known as Therapeutic Use Exemption (TUE), a number of conditions needed to be fulfilled before a TUE could be granted. These were:

- the athlete would experience significant impairment of health if the prohibited medication was withheld;
- no enhancement of performance would result from the administration of the prohibited substance as medically prescribed;
- no permitted and practical alternative medication could be substituted for the prohibited substance.

The TUE concept, based on these criteria, was approved by the IOC in 1992 and TUEs for oral glucocorticosteroids for inflammatory bowel disease were first granted at the 1992 Barcelona Olympic Games. When the World Anti-Doping Code was approved in March 2003, concept of TUE was included and subsequently an International Standard for TUE was approved later in 2003 [45].

There are only two anabolic agents for which TUEs may be approved: T and danazol. There are two medical conditions that may warrant a TUE for danazol. One athlete competed at the 1996 Olympic Games having been granted a TUE for danazol with documented genetic deficiency of C-1 esterase inhibitor causing life threatening hereditary angioneurotic edema. The other condition is more common and is disabling endometriosis which has not responded to all permitted methods of treatment including surgery and must be on the recommendation of a gynaecologist. Because danazol is anabolic and has potential to enhance performance in females, the duration of all approvals for endometriosis should be for a maximum of 3–6 months. In 2004, a yachtsman participated at the Olympic Games, having been granted a TUE for T initially in 1995 for bilateral orchidectomies due to carcinomas but he had failed to qualify for the 1996 and the 2000 Olympic Games.

14 Conclusion

The misuse of AAS by athletes at the Olympic Games commenced some years before these substances were prohibited in sport in 1974. When subject to doping controls, AAS remain the commonest category of pharmacological agent detected in athletes' urines and at Summer Olympic Games of 2000 and 2004. The contest between anti-doping agencies and doped athletes and their pharmacological and medical supporters has continued for several decades and shows no sign of diminishing. Endocrinologists need to be mindful when confronted by athletes who seek T replacement for low-normal or age-reduced serum T levels. Occasionally, athlete-patients will be encountered who have a completely valid justification for T replacement therapy and the TUE system is designed to serve their medical needs while defending the fairness of elite sports.

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