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## The history of doping and growth hormone abuse in sport

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### ABSTRACT

The earliest records of doping in sport come from the Ancient Olympics games when athletes are reported to have taken figs to improve their performance. With the advent of modern pharmacology in the 19th century, many athletes began to experiment with cocktails of drugs to improve strength and overcome fatigue. As this practice was not illegal, there are good records of the lengths athletes would go to in order to win. Alongside the benefits, came the dangers and following several fatalities, a code to ban performance enhancing drugs was gradually developed.

Growth hormone was first isolated from the human pituitary gland in the 1950s. Its anabolic effects were soon recognised and athletes had begun to abuse it by the early 1980s, at least a decade before it was used therapeutically by adult endocrinologists. A number of high profile athletes have admitted using growth hormone. Detection of its abuse has been challenging and the lack of an effective test has undoubtedly encouraged its abuse. Only now are methodologies being developed that should stem this tide.

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### 1. Introduction

When humans are placed in a competitive setting, particularly in the field of sport, they will attempt to gain an advantage over their opponent in order to achieve superiority and win the competition. The earliest records of methods employed by athletes to gain an advantage come from the ancient Games, as early as 668 BC, when athletes studied the effects of special diets on their performance [1]. More recently the sporting industry has capitalised on the desire for superiority among athletes by spending millions of dollars a year to improve sporting equipment and apparel. Similarly many professional sports trainers publish training guides promising to teach athletes the “winning principles” through their training methods.

These methods are legal and even desirable but when all legitimate methods have been implemented and the athlete has reached their peak performance, there is a temptation to seek out pharmacological methods to improve performance yet further. While drugs can improve athletic performance, the use of such drugs is prohibited for several reasons: first the use of performance enhancing drugs is harmful to the athlete and the athlete may not be in a position to give fully informed consent to receive the drugs as happened in the former East German republic [2]. Second, the use of performance enhancing drugs makes the competition ineq-

uitable. This argument is potentially flawed as if all had equal access to drugs then the “playing field would be levelled” and furthermore not all athletes have the same access to training facilities and nutritional support as others but this is not considered unfair. Finally athletes are role models within society and if it is perceived that only through performance enhancing drugs can aspiring young people reach the pinnacle of their sport, this will lead to a wider use of such drugs and the potential for harm extends beyond professional athletes to the wider society.

### 2. Early history of doping

Despite the perception that doping is a modern phenomenon, there are many examples of substance use by ancient people, including extracts derived from plants, animals or even humans.

One of the first performance enhancing substances to be tried was testosterone. Having identified the properties of this hormone by examining the behaviour of their animals following castration, the ancients were reported to eat the testes of other animals or humans to improve or heal their own [1].

The importance of diet on performance was also recognised; one of the earliest reports describe the use of a diet of dried figs to improve the performance of Charmis, the Spartan winner of the stade race (~200 yards [183 m]) at the Olympic Games of 668 BC [1].

The Ancient Greeks were also the first to use stimulants in the form of potions of brandy and wine as part of their sport training routine [3]. The Roman gladiators also used unspecified stimulants to overcome fatigue and injury [3]. Most of these stimulants were

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derived from plants. Examples include the use of bufotein, a drug derived from the muscarine containing mushroom, fly-garic (*Amanita muscaria*), *Cola acuminata* and *Cola nitida* and coca leaves.

### 3. 19th Century developments in the use of stimulants and anabolic agents

The number and types of drugs and substances used to improve performance in the latter half of the 19th century escalated, in line with development in modern pharmacology and medicine. Stimulants were now primarily used as ergogenic aids to improve muscular work capacity while the anabolic effects of substances that were later classified as hormones began to be recognised.

Caffeine was the main substance used in this period to improve brain functioning. Alcoholic drinks were also considered useful as a stress relief aid. As there were no rules prohibiting such substances, athletes did not try to conceal this, and as a result, there are good records on doping from this time. Trainers also developed their own doping recipes, using combinations of various stimulants, such as strychnine tablets, mixtures of brandy and cocaine.

In the 19th century, the continuous “Six Day” bicycle races began, requiring athletes to have great physical strength and stamina. A variety of performance enhancing mixtures were tried; there are reports of the French using mixtures with caffeine bases, the Belgians using sugar cubes dripped in ether, and others using alcohol-containing cordials, while the sprinters specialised in the use of nitro-glycerine [1,4]. As the race progressed, the athletes increased the amounts of strychnine and cocaine added to their caffeine mixtures. It is perhaps unsurprising that the first doping fatality occurred during such an event, when Arthur Linton, an English cyclist who is alleged to have overdosed on “tri-methyl” (thought to be a compound containing either caffeine or ether), died in 1886 during a 600 km race between Bordeaux and Paris [4]. There is some dispute over this, as others [5] suggest that Linton actually won this race and did not die until 10 years later from typhoid fever!

There were reports that mixtures of champagne, brandy, hot drops of morphine, belladonna and strychnine were used to maintain high levels of strength and energy during another endurance race, the “ultramarathon” which was a walking and running race over 6 days and 6 nights, with the winner being the person who covered the greatest distance [6].

Around the same time in 1889, Charles Édouard Brown-Sequard reported the effects of a three-week programme of self-injections of “first, blood of the testicular veins; secondly semen; and thirdly juice from a testicle... from a dog or a guinea pig” to the Society of Biology in Paris [7]. Shortly after in 1894 Oskar Zoth and Fritz Pregl assessed the effect of testicular extracts on muscular strength as a means of improving athletic performance [1].

### 4. 20th Century doping

At the beginning of the 20th century, scientists isolated, characterised, and synthesized testosterone and gained an understanding of its anabolic effects. The first recorded case of the use of testosterone as a means of improving performance was in 1941 in an 18-year-old horse named Holloway, who won many races with improved performance following treatment [8]. Sport trainers soon realised the potential of testosterone and other anabolic steroids and began to advocate their use. Photographs of body-builders showing deformed body shapes and extremely large muscles are highly indicative of testosterone and anabolic steroids use at this time.

Although amphetamines were first identified in 1887, the use of these stimulants only began to increase in the mid 1930s. While

the benefits were first appreciated by servicemen fighting in the Second World War and college students, athletes quickly included amphetamines in their “drug diet” [9,10].

The use of stimulants was particularly prevalent in cycling; the 1960s and 1970s were deemed as the “amphetamine decades” for anyone competing in cycling. The first televised doping fatality occurred during the 1967 Tour de France, when the English cyclist, Tom Simpson, died with high circulating levels of methamphetamine.

In 1980s, anabolic steroids and cortisone were mainly used but latterly the number of drugs used by athletes has expanded dramatically and the current World Anti-Doping Agency list of prohibited substances extends over several pages and includes several categories of drugs, including anabolic agents, hormones, diuretics and masking agents, stimulants and narcotics as well as prohibited methods such as blood transfusion.

Erythropoietin (EPO) and blood transfusion have been used to improve the oxygen carrying capacity of the blood and just hours before the 2000 Tour de France was to begin, three cyclists failed a mandatory EPO test and were expelled from competition. In Barcelona, an athlete was given an incompatible blood transfusion collapsed, required dialysis and nearly died.

By the early 1980s and beyond, the use of human growth hormone had also become well established on the body building community’s drug menu.

Doping moved onto a higher plain during the 1970s and 1980s when there were suspicions that several countries pursued state-sponsored doping. These doubts have been substantiated in the former German Democratic Republic, where Ph.D. programmes were established to develop the ideal regimens to improve performance [11].

### 5. Doping at the Olympic Games

Prior to the introduction of doping regulation, there were ample reports of the use of performance enhancing drugs during the modern Olympic Games. In 1904, Thomas Hicks, winner of the marathon, took strychnine and brandy several times during the race. At the Los Angeles Olympic Games in 1932, Japanese swimmers were said to be “pumped full of oxygen” [12]. Anabolic steroids were referred to by the then editor of Track and Field News in 1969 as the “breakfast of champions”.

In the decades to follow, as doping regulation was introduced, the use of performance enhancing drugs changed rather than decreased and became more secretive. At the 1988 Seoul Games, the disqualification of Ben Johnson, who tested positive for stanazol, an anabolic steroid, led to a subsequent investigation that concluded that “at least half of the athletes who competed in Seoul used anabolic steroids to enhance their performances” [13]. Subsequent testing and inquiries have shown that at least six of the Seoul men’s sprint finalists used drugs at some point in their careers. Eight years later, the 1996 Atlanta Olympic Games were termed the “Growth Hormone Games” by some athletes [1] while the 2000 Sydney Olympic Games were nicknamed the “Dirty Games”, because of the large number of articles discussing performance enhancing drugs at the games.

Marion Jones, the US sprinter and winner of three gold and two bronze medals, was disqualified in October 2007 after confessing that she had taken tetrahydrogestrinone (THG) from September 2000 till July 2001. The IOC formally stripped Jones of her 5 medals. On 2 August 2008, the International Olympic Committee stripped the gold medal from the US men’s 4 × 400 m relay team, after Antonio Pettigrew admitted using a banned substance. Three of the four runners in the event final, including Pettigrew and twins Alvin and Calvin Harrison, have admitted or tested positive for

performance enhancing drugs, as well as Jerome Young who competed in a preliminary round.

Twenty-four doping violations were reported at the 2004 Athens Olympic Games, twice as many as at the Los Angeles Olympic Games in 1984. Most recently at the 2006 Winter Olympics in Turin, police officials confiscated suspect medical equipment from the residence of Austrian athletes, which included several packs of drugs, and blood transfusion equipment.

By comparison, there were relatively few doping violations at the 2008 Beijing Olympic Games.

## 6. How prevalent is doping?

The true prevalence of modern doping is unknown because of the secrecy surrounding it. Around 1% of tests undertaken the WADA accredited laboratories are positive but this is the most conservative estimate because of the stringent efforts made to avoid false positive results and the intermittent nature of testing [14].

In 2000, the US Office of National Drug Control Policy concluded that the doping epidemic varied widely from 10% to 90% of the athletes. The high financial stakes for Olympic athletes, corporate sponsors, the TV broadcast and cable industries and sport governing bodies, coupled with the pharmacopoeia of performance enhancing substances, the athlete's drive to win, and the absence of an effective policing mechanism were all seen to be encouraging athletes to use prohibited substances [1,15].

## 7. Growth hormone doping

Growth hormone was first extracted and purified from the human pituitary glands in 1956 (Fig. 1) [16]. It was shown to promote growth in hypopituitary animals and was soon used to treat children with hypopituitarism, dramatically restoring growth [17]. The beneficial effects in adults were first observed as early as 1962, when GH was noted to increase vigour, ambition and sense of well-being in a woman with adult hypopituitarism [17].

Cadaveric growth hormone was the only source of the hormone until 1987 when the first recombinant version (methionyl human GH) became available. The recognition that pituitary-derived GH was a source for the prion-induced Creutzfeldt–Jacob Disease led

to its withdrawal from the market place in 1985 [17] although supplies of pituitary-derived GH continue to be available on the black market to this day.

How and where GH was first used as a doping agent is unknown but the earliest publication to draw attention to it was Dan Duchaine's "Underground Steroid handbook" which emerged from California in 1982 [18]. Although this book contains some fundamental errors, such as the recommendation and advertisement of animal GH for use in humans, the description of GH actions in this article was remarkably accurate and pre-dated adult endocrinology experience by about a decade. GH was described as the "most expensive, most fashionable and least understood of the new athletic drugs. It has firmly established itself in power-lifting and within a few years will be a commonly used drug in all strength athletics." The book also specifically states, "Wow, is this great stuff! It is the best for permanent muscle gains. . . People who use it can expect to gain 30 to 40 pounds of muscle in ten weeks." [18].

Duchaine was regarded as an expert in the body building community as the "steroid guru" and was responsible for the development of many doping trends. Through experimentation on himself and other body builders he was coaching, he advised athletes on the best substances and combinations to use for the optimal performance results.

It is interesting to note that it was not till much later that the role of GH in regulating body composition in human adults in such a way that it might be regarded as a new anabolic agent was appreciated by the medical profession [19,20]. Thus, as is often the case in the history of sport, the athletes got there before the scientists!

Duchaine later retracted his views on GH, as he could not find any scientific studies to support his claims and in his later book published in 1993 "Ultimate muscle mass" he stated that "I'd guess that almost 90% of all athletes taking STH [growth hormone] got no anabolic results from it (this includes at least two Mr. Olympia competitors)" [18,21]. Although there has been considerable debate about the performance enhancing properties of GH [22], as it turns out, Duchaine's initial observations were almost certainly correct as recent studies have shown that GH exerts a performance benefit in abstinent anabolic steroid users as well as healthy older men [23,24].

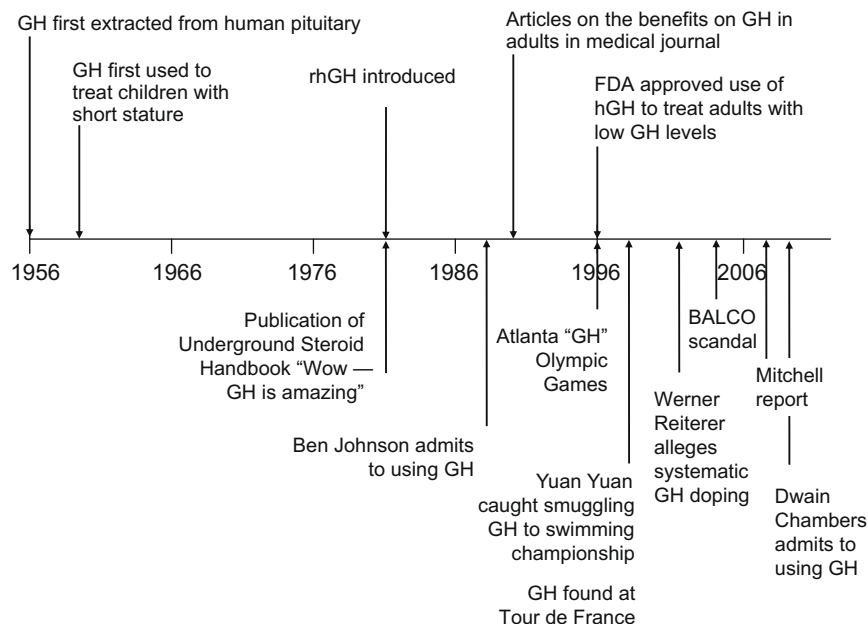


Fig. 1. Time-line of GH in clinical practice and abuse by professional sportsmen and women.

The most famous case of GH abuse in professional athletics came to light in 1988 following Ben Johnson's amazing win in the 100 m final at the Olympic Games in Seoul. After his subsequent disqualification when stanozolol was detected in his urine, both he and his coach Charley Francis admitted under oath at a later hearing that he had taken human GH in addition to anabolic steroids perhaps explaining how he managed to develop such delroids [25,26].

Following the 1988 Seoul Olympic Games doping scandal, Justice Charles Dubin, head of this enquiry, conducted one of the most searching investigations in history into the abuse of drugs in sports. During these hearings, the Canadian sprinter Angella Issa-njenko also admitted using hGH along with other drugs. According to the 900-page Dubin inquiry report [13], it was concluded that the tight regulations of the use of GH had not prevented it from becoming available to athletes.

It is impossible to determine the precise prevalence of GH abuse amongst sportsmen and women as much of our evidence comes from anecdotal reports [27]. Although initially advocated for strength disciplines, endurance athletes are also attracted to GH's lipolytic actions and reduced fat mass and in 1988 a large quantity of GH was found in a team car at the Tour de France [28].

The International Olympic Committee included GH in its prohibited substance list in 1989 as part of a new doping class of "peptide hormones and analogues" despite the lack of a legitimate test for hGH [29]. This did not seem to deter use of GH as a performance enhancing substance and for many athletes, it became the new drug of choice [12].

There is evidence that adolescents are using GH. In a survey of two US high schools, 5% of male students admitted to having taken GH and nearly one-third knew someone who had taken GH [26]. Most GH users were unaware of its side effects and reported their first use between 14 and 15 years of age.

Growth hormone destined for therapeutic use has ended up in athletes' possession and there are reports of parents selling GH prescribed to treat their child's GH deficiency on the black market. At the 1998 World Swimming Championships, Yuan Yuan, a Chinese swimmer, was stopped on entry into Perth with a suitcase full of GH that had been exported to China for therapeutic reasons.

A few athletes have admitted to taking GH. In a death bed confession, Lyle Alzado, an American football player admitted that 80% of American footballers have taken GH. In 2000, Australian discus champion Werner Reiterer claimed institutional and supervised usage of GH. With this in mind, it is interesting to note that 6 months before the Sydney Olympic Games, 1575 vials of GH were stolen from an importer's warehouse in Sydney.

Track stars Marion Jones and Tim Montgomery, and National Football League players such as Bill Romanowski, and sluggers including Barry Bonds, Gary Sheffield and Jason Giambi, are amongst some of the athletes who have been recently alleged to be taking growth hormone in the controversial book "Game of Shadows", which was written following undercover investigations by two San Francisco reporters [30].

Recently, Victor Conte, the owner of the Bay Area Laboratory Co-Operative (BALCO), claimed that he had supplied GH to many high profile American athletes including Tim Montgomery and Marion Jones. This admission came after the raid on BALCO's headquarters on 3 September 2003, when evidence of systematic doping was found and many of the top names in athletics, baseball and American football were implicated in the scandal. Although many have denied taking GH, Tim Montgomery allegedly admitted to taking GH before a US Federal grand jury and later faced a 2 year ban for doping offences. Marion Jones, 5 times Olympic medal winner, admitted in 2007 to the use of performance enhancing drugs, including growth hormone. She was later sentenced to a 6-month jail sentence for falsely denying administering performance

enhancing substances. Conte was imprisoned for four months for his role in the scandal [30].

Most recently Dwain Chambers, who was also implicated in the BALCO scandal and was banned from competing for 2 years for testing positive for THG, attempted to overturn his lifetime Olympic ban by cooperating with the UK authorities and providing them with information about his doping regimen which included rhGH.

The conclusion of Senator Mitchell's enquiry into doping in baseball in 2007 concluded that GH abuse is widespread and players had switched to GH because it is undetectable [31]. The report states that players who use human growth hormone did so because they believed that it assisted their ability to recover from injuries and fatigue during the long baseball season; this also is a major reason why players used steroids.

GH can be readily bought over the internet and a recent investigation by Matthew Pinsent, ex-Olympic oarsman now working for the British Broadcasting Corporation demonstrated that the batch that he purchased was pure. One of the authors (RIGH) has appeared on "Richard & Judy", a UK television chat show with one of the richest men in the UK who claims to be spending thousands of pounds a month on GH in an attempt to increase his life expectancy and physique. Conversations during the show suggested that this was not an isolated incident. The recent conviction of Sylvester Stallone who was caught with GH in his possession on entering Australia only confirms that GH is readily available in athletic and body building circles.

## 8. History of anti-doping

Although the use of performance enhancing drugs is unethical and prohibited by the World Anti-Doping Agency, defining which drugs and methods constitute doping is a major challenge. Even the origin of the word "doping" is controversial. Some claim that the word doping is originally derived from the African Kaffirs who used local liquor called "dop" as a stimulant [1,27,32]. Others claim that the word "doping" originates from the American expression "dope", a slang word for opium, since in the days when doping of horses was first attempted opium was the most common used substance [33].

Although the earliest reports of doping come from Ancient Greece and the original Olympic Games, interestingly this was not considered to be cheating at the time while other offences such as bribing an official were treated with considerable gravity. Athletes violating Olympic rules were banished for life from the games and had their names inscribed on stone pedestals lining the entrance of the Olympic stadium, along with the names of their families and the details of their offence.

The use of performance enhancing substances was considered for the first time as inappropriate as late as the end of the first World War [12]. There was little attempt to prohibit the use of performance enhancing substances in a sport competition setting until the 1920s, and even less attempt was made to discourage such use with Dr. Otto Rieser, in his work "Doping and Doping Substances", being the first to do so in 1933 [1].

In 1928, the International Amateur Athletic Federation (IAAF) was the first international sport body to ban the use of doping, in this case the use of stimulating substances. Others followed the IAAF lead but in the absence of effective tests, these measures did not curb the use of drugs.

In 1966 the International Cycling Union and International Federation of Association Football introduced anti-doping tests for the first time and in the following year, the International Olympic Committee established its Medical Commission and first voted to adopt a drug-testing policy banning the use of specific drugs. Drug tests were first introduced at the Olympic Winter Games in Grenoble and at the Olympic Games in Mexico in 1968. Despite

this initiative, few sporting organisations had the necessary protocols or equipment to enforce the bans [1]. Consequently it was 15 years before the first anti-doping was undertaken by the National Football League in 1982.

Over the years, the IOC has reviewed its Prohibited Substances List several times, and today this is enforceable at all Olympic events [1]. While the Prohibited Substances List is extensive, it does not apply at all sporting events and many professional sports either do not test at all or have programmes that are substantially less rigorous than the IOC programme.

The IOC Medical Commission (IOC MC) was established under the chairmanship of Prince Alexander de Merode who had absorbed a considerable amount of medical and scientific knowledge through his lifetime dedicated to building the anti-doping structure of the IOC. In this activity, he had a stalwart scientific partner in Professor Manfred Donike and between them they developed a world-wide network of top class laboratories staffed by top grade chemists and pharmacologists, who were equipped to measure mainly steroids and stimulants in urine.

The introduction of a reliable test method for anabolic steroids was finally achieved in 1974 and this resulted in a marked increase in the number of drugs disqualifications in the late 1970s, notably in strength-related sports such as throwing events and weightlifting. This coupled with the introduction of out-of-competition testing has reduced the use of these drugs. It is interesting to note that several Olympic records are still standing from times before the introduction of effective testing, illustrating the potency of the drugs and effect of rigorous testing.

A major setback in the fight against doping occurred in 1998, when a large number of prohibited medical substances were found by police in a raid at the Tour de France. Following this scandal, IOC decided to convene a World Conference on Doping in Lausanne on 2–4 February 1999, with the aim of bringing together all stakeholders involved in the fight against doping. A major outcome of the conference was the recognition of the need for an independent international agency, which would set unified standards for anti-doping work and coordinate the efforts of sports organizations and public authorities. As a direct result, the World Anti-Doping Agency (WADA) was established on 10 November 1999.

The development and implementation of a uniform set of anti-doping rules, the World Anti-Doping Agency Code, together with the list of banned substances is seen as one of the most important achievements to date in the fight against doping in sport.

## 9. The fight against growth hormone doping

Although prohibited in 1989, further action to implement the ban on GH was not undertaken till 1991, when Professor Manfred Donike (Secretary of the IOC MC Sub-Commission Doping and Biochemistry in Sport) on behalf of Prince de Merode invited one of the authors (PHS) to join the Sub-Commission as an advisor on GH.

At this time, the IOC had only limited experience in dealing with complex protein and glycoprotein hormones with only the immunoassay of human chorionic gonadotrophin (hCG) in urine in existence. Similarly, the IOC had virtually no knowledge of the issues around the development of a test for detecting GH abuse and this coupled with several cultural issues, discussed below, hampered the development of a test.

The first issue was the requirement for blood rather than urine testing as previously all testing had been performed on urine samples. In fact blood testing was introduced a year later at the Lillehammer Olympic Games in 1994 to detect of 'blood doping' by heterologous blood transfusions. Much to the surprise of those strongly opposed to blood testing, the whole process ran smoothly and was more convenient for the athlete than conventional urine testing.

The second hurdle was the concept of a need for scientific research to develop a suitable test. There was a general feeling within the IOC that research undertaken in athletes was unacceptable because of the need to protect the athletes.

Although a greater understanding for the need for research was eventually obtained, a further issue arose because the IOC did not fund research, in particular 'invasive' clinical science and it was unclear where alternative suitable funding could be found. Conventional medical research, such as research councils or charities, and industry were not interested in funding such research. This presented a problem as this was a clear example of 'commissioned' research where the appropriate 'commissioner' was not prepared to find the resources needed as they felt that this was not their role.

Eventually, following lobbying from Prince de Merode and the IOC Member (now President) Jacques Rogge, the research arm of the European Union (EU) agreed to include anti-doping research in its Biomedicine and Health (BIOMED 2) research programme.

This opportunity led to the conception of the GH-2000 project which comprised a consortium of leading endocrinologists from four European countries with expertise in GH research, led by Peter Sönksen, in partnership with two [pharmaceutical companies manufacturing GH (Novo Nordisk (DK) and Pharmacia (SE)), statisticians from the University of Kent (UK) and The IOC Medical Commission.

The conclusion of the GH-2000 project was a proposal for a test based on the measurement of two GH-sensitive markers, IGF-I and type III pro-collagen (P-III-P) [34]. The test was relatively straightforward in scientific terms and exhibited very good sensitivity at a specificity of approximately 1 in 10,000 to detect those taking GH with a window of opportunity that could last as long as 14 days after the last injection of GH.

The project reported its results to the EU and IOC on 20th January 1999 [35] and in response the IOC organised a workshop in Rome in March 1999 with invited outside experts from around the world to review critically and quality assure the results.

The workshop strongly supported the proposed test but it was recognised, however, that further research was needed to ensure that the test worked in non-Caucasian ethnic groups and the test was not affected by injury. A further issue arose because IGF-I and P-III-P had been measured by commercially available assays for the GH-2000 project and a need for the IOC to develop its own immunoassays was recognised.

Following the meeting, the IOC initially agreed to fund this further work but this offer was subsequently withdrawn without explanation and the project went into limbo. This was a major disappointment and whatever the reason, one has to question the IOC decision that not only prevented the test being ready for the Sydney Olympic Games in September 2000 but also meant that implementation has still not taken place 10 years later.

Around the same time, Professor Christian Strasburger and Martin Bidlingmaier were developing a method based on the measurement of GH isoforms with funding from the IOC. Pituitary GH contains many isoforms while recombinant human GH consists of only 22 kD [36]. When rhGH is administered, endogenous GH secretion is inhibited and the ratio of 22 kD GH to total GH increases [37]. This research led to the introduction of the isoform test at the Olympic Games in Athens in 2004, in Turin (2006) and recently in Beijing (2008). No positive tests were detected but this was perhaps unsurprising as this method has a relatively short window of opportunity of less than 24 h. Thus any athlete who ceases GH on the day before the test will not be detected. Arguably, however, the optimal, if not only, use of this method must be in unannounced 'out of competition' testing.

Work on the marker approach was eventually resumed in 2003 after several unsuccessful bids for further funding and after the establishment of the US Anti-Doping Agency (USADA), who had

sufficient funding to commission GH research which was high on their list of priorities. The GH-2004 project became established at the University of Southampton but continued its close collaboration with Dr. Eryl Bassett (University of Kent) and Professor David Cowan (Head of WADA Laboratory, King's College, London) to address the issues raised in Rome in 1999. The project subsequently received supplementary funding from WADA who were particularly interested in contributing to the funding of the aspect of ethnic effects.

The outcomes of the GH-2004 project have been reported to WADA and USADA and have demonstrated that while there are minor ethnic differences and effects of injury, these did not affect the performance of the test [38].

At the same time as the GH-2004 project was on-going, Professor Ken Ho and colleagues established an Australian-Japanese Consortium to develop a test for GH. This group provided further evidence of the strength of the marker approach to detect those taking GH, and showed that the co-administration of anabolic steroids did not reduce the sensitivity of the test [39]. A study undertaken in Germany by a group led by Dr. Astrid Kniess provided more evidence that the marker approach and GH-2000 test worked to detect those taking GH [40].

Given this wealth of evidence, one has to question why WADA have not implemented the test which is complementary to the isoform test and has the advantage of a longer window of opportunity and the ability to detect cadaveric GH. The major stumbling block appears to be the need to use commercial assays and the difficulties in converting between assays to fulfil the WADA rule that states that two immunoassays are required for each analyte to be measured and that the antibodies in these immunoassays should recognise different epitopes [41].

Although the need for the IOC and then WADA to have its own assays was recognised in Rome in 1999, this work is yet to be completed. The Institute for Bioanalytics (IBA) based in CT, USA was successful in obtaining funding from USADA in 2000 to develop two 'in-house' immunoassays for both IGF-I and P-III-P but unfortunately underestimated the difficulty of the project. By the time the grant was used up, the project had not been completed and further approaches for funding were unsuccessful.

As forecast in the GH-2000 Final Report assay, manufacturers changed their products with little or no warning. Between the completion of GH-2000 and start of GH-2004, the Nichols IGF-I radioimmunoassay used in the GH-2000 project had been changed to a radiometric assay and even this was subsequently withdrawn. Consequently the GH-2004 project needed to use two new commercial assays. There are only two commercially available P-III-P assays but as there is no international reference preparation, these assays measure in different units. The GH-2004 project has shown excellent correlation between the two assays for each analyte with the scatter being no more than would be expected from between assay variability.

## 10. Conclusion

Doping has occurred for many years in sport and there are no signs that this is decreasing. As testing regimens improve, the agents used by athletes changes in order for them to elude detection. Growth hormone has been abused for its anabolic and lipolytic properties for over 20 years by athletes seeking to obtain a competitive advantage. The precise prevalence rates are unclear because of the secrecy surrounding its use but anecdotal evidence points to a widespread availability. The detection of GH is certainly lagging behind its use. The authors would like to acknowledge the team effort that has gone into the various projects aimed at detecting GH. It has been a long journey and we are not there yet.

## Conflict of interest statement

The authors are all investigators in the GH-2004 project and have received funding from WADA and USADA to undertake the development of a test to detect GH.

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