Revised or New Test Procedures: What CAS Requires

by **Richard H. McLaren***

Introduction

The World Anti Doping Code, {the WADA Code} that applies to all Summer Olympic sports, came into effect just in time for the opening of the "Welcome Home" Olympic Summer Games in Athens, Greece in August 2004.[1] Since that time, challenges to the Code have become more numerous and increasingly complex. One of the more common tactics in these challenges has been to attack both the revisions to established testing procedures and the introduction of new testing procedures by WADA accredited laboratories. This paper explores what limitations, if any, have been imposed on the use of revised or new testing procedures established by WADA for legal purposes. Revisions to the testing procedures for nandrolone and erythropoietin, - two prohibited substances - as well as the introduction of a new testing procedure for blood doping by transfusion, illustrate the challenges to the legal mettle of the Court of Arbitration for Sport {CAS} brought about by greater scientific understanding. The test procedure for nandrolone was originally based on the premise that there was no naturally occurring production of the substance[2] in the human body. However, thanks to the evolution of scientific understanding, the scientific community has recognized that nandrolone is produced naturally in the body in small quantities, a discovery that has required an adjustment in the laboratory testing procedure[3] by the implementation of a threshold limit for the substance. The year 2005 brought with it the recognition that a phenomenon described as "active" urine requires another refinement in the test procedure.[4] A similar evolution of scientific understanding has occurred with respect to the test procedure for erythropoietin. By virtue of studying these testing developments we can explore the following theme: Can progress in testing continue in light of the CAS requirements? The same proposition and theme is also addressed by examining what was required to accept the introduction of flow cytometry as an analytical technique for detection of the prohibited method of homologous blood transfusion in the case of Tyler Hamilton.[5]

In light of these developments, the challenge for CAS will be both in accommodating revisions and in permitting the introduction of new testing procedures to deal with new situations. In so doing, the cost and process of legal acceptance for new procedures cannot continue to be as expensive. The accommodation of change and innovation must be realized while ensuring the protection of athlete's rights.

1. Nandrolone

Nandrolone (also referred to as 19-nortestosterone) is an anabolic-androgenic steroid used to build muscle mass and is a prohibited substance under the WADA Code. In addition to the substance itself, there are nandrolone precursors such as 19-norandrostenedione, 19-norandrostenediol and norethisterone, that are also prohibited substances that are easily purchased as dietary supplements.[6] Upon entering the body, these precursors may be metabolized into nandrolone and produce the same metabolites as if nandrolone had been directly ingested.

Following consumption, nandrolone is quickly metabolized by the body which requires that the detection procedure be based upon testing for the presence of nandrolone metabolites that are then excreted in the urine. The major metabolite of nandrolone that is currently tested for is 19-norandrosterone {19-NA}.[7] It was initially thought that 19-NA was not produced endogenously in the body. Based on this premise, the presence of 19-NA in a sample, in any amount, had indicated the administration of a prohibited substance. However, in 1996, with the introduction of gas chromatograph/mass spectrometery {GC/MS} technology that could detect even minute quantities of substances such as 19-NA, it was quickly understood that low concentrations of 19-NA could be produced endogenously.[8] Published scientific studies later confirmed the endogenous production.[9] The endogenous production of 19-NA was first recognized in pregnant females,[10] but eventually it was determined that endogenous 19-NA could be produced in males as well.[11] As the scientific understanding of 19-NA grew, guidelines emerged, developed by various laboratories such that a positive result would not be reported unless the concentration of nandrolone in a urine sample exceeded set levels.[12]

a. The Early CAS Jurisprudence

The acknowledgement by the scientific community and anti-doping bodies that nandrolone metabolites could be produced endogenously initially led to some confusion in nandrolone cases decided by CAS. Part of the problem was a lack of proper codification of the allowable limits for 19-NA. Additionally, the state of scientific knowledge at the time suggested that low concentrations of 19-NA should be interpreted cautiously. There were three CAS cases involving nandrolone heard

* Professor Richard H. McLaren, Western Law Faculty, University of Western Ontario, London, Canada. An early version of this paper was presented to the Play the Game conference on 9 November 2005 at Copenhagen, Denmark. I would like to acknowledge the very capable and significant assistance of my researchers Matthew Atkey and Brinn Norman, Western Law Class of 2007 and of my son Joshua McLaren, M.A. (U.W.O.) for his proof reading and suggestions at reorganization in the late stages of developing this paper.

1 For a discussion on the procedure and jurisprudence of CAS and its evolving application to the provisions of the WADA Code see Richard McLaren, "CAS Doping Jurisprudence: What Can We Learn" (2006) 6 I.S.L.R. 4 (Sweet & Maxwell, London).

2 As discussed in *Bernhard v/ITU* CAS 1998/222 at para. 10 {"*Bernhard*"}.

3 For scientific papers recognizing human production of nandrolone in small quantities see Le Bizec B, Monteau F, Gaudin I, Andre F. "Evidence for the presence of endogenous 19-norandrosterone in human urine." (1999) 723 J Chromatogr B. Biomed Sci Appl. 157-72. Dehennin, L., Bonnaire. Y., Plou, P. J. "Urinary excretion of 19-norandrosterone of endogenous origin in man: quantitative analysis by gas chromatography-mass spectrometry." (1999) 721 J Chromatogr B. Biomed Sci Appl. 301-07. To view WADA's detection limits for Nandrolone see WADA Technical Document TD2004NA, "Reporting Norandrosterone Findings"; p. 2.

4 WADA Explanatory technical note: stability of 19-norandrosterone finding in urine May 13, 2005. ["Explanatory Note"].

5 *Tyler Hamilton v/ USADA & UCI* CAS 2005/A/884, issued 10 February 2006 {"*Hamilton*"}.

6 The IOC Medical Code Prohibited Class of Substance under *anabolic Agents (class C)* was expanded to include these substances as at 31 January 1999. See IOC Medical Code January 1999 & Supplement 2000. See *Nandrolone Review* A Report to UK Sports Council From the Expert Committee Chaired by Professor Vivian James, in January of 2000. See www.uksport.gov.uk. {"Nandrolone Review"}.

7 Nandrolone Review, *supra* note 7 at para. 8.

8 See *Bernhard, supra* note 3 at para. 10.

9 Le Bizec et al., *supra* note 4.

10 Resnik, Y., Herrou M., Dehennin, L., Lemaire, M., Leymarie,. P. "Rising plasma levels of 19-nortestosterone throughout pregnancy: determination by radioimmunoassay and validation by gas chromatography-mass spectrometry" (1987) 64(5) J Clin Endocrino Metab. 1086-8.

11 Le Bizec et al., *supra* note 4.

12 These guidelines which established thresholds for the presence of 19-NA were initially set out in a document entitled *Analytical Criteria for Reporting Low Concentrations of Anabolic Steroids (August 1998)* {"Analytical Criteria"} produced by a subcommittee of the IOC Medical Commission. They can be found as an appendix to *Nandrolone Review* a report to UK Sport in January of 2000. See www.uksport.gov.uk. These guidelines had the nature of a recommendation addressed to the IOC laboratories and did not constitute a legal rule. See *Bernhard*, supra note 3 at para. 11.

in 1998 which involved discussion of a "grey zone"[13] where the concentration of 19-NA falls between 2 ng/mL and 5 ng/mL in men.

During the hearing in *Mason*,[14] the first of these cases, there was testimony that uncertainty existed among experts as to the maximum concentration of nandrolone produced by the human body. Some scientists were skeptical about whether concentrations of nandrolone metabolites found in the "grey zone" would be sufficient evidence to assume a doping offence. It was thought at the time that further investigations would be required in order to confirm a positive result in the "grey zone". However, in the case of *Mason*, there was greater than 5 ng/mL of 19-NA in his sample, which was above the "grey zone", and he was found to have committed a doping offence. In the next case, *Bouras*,[15] there was further reference to a cautious area between 2 ng/mL and 5 ng/mL; however, Bouras tested over 5 ng/mL for nandrolone.

The "grey zone" doctrine had a more significant effect in the case of Olivier Bernhard,[16] a Swiss triathlete who had a positive test for nandrolone where his A sample had 3 ng/mL of 19-NA. His B confirmed that there was 19-NA present in the urine, but there was no reported concentration for that sample. In an attempt to prove that the 19-NA in his urine was produced endogenously, Bernhard had further independent testing for nandrolone carried out on himself. This testing indicated that Bernhard endogenously produced between 2 and 3 ng/mL of 19-NA. The Panel in *Bernhard* stressed that the threshold of 2 ng/mL for 19-NA set out by the IOC Medical Commission had the nature of a laboratory recommendation or presumption, and not a legal rule. The Panel stated:

> It is therefore appropriate to determine whether the actual state of medical science still allows a conclusion or, at least, permits a presumption that the existence of nandrolone metabolites in the urine result from external application of nandrolone.[17]

Thus it appears that CAS may not accept scientific presumptions regarding testing procedures that are found to be contrary to the actual state of medical science.

Interestingly, the Panel found that it was beyond scientific doubt that low concentrations of nandrolone metabolites falling within the "grey zone" can be the result of endogenous production of the human body. The evidence indicated that there was a remote and decreasing probability that the 19-NA present has been produced endogenously as its concentration increased through the "grey zone". The legal impact of this finding was that the scientific presumption of a doping offence when the 2 ng/mL threshold was exceeded could not be considered to be absolute and irrebutable and could not be upheld. Therefore, in situations where the concentration of 19-NA falls within the "grey zone", the Panel held that sanctioning bodies were required to provide additional evidence in support of the presumption of an offence, or to at least exclude all other causes. Since the ITU had not presented such evidence, while Bernhard had presented evidence to rebut the scientific presumption, the Panel did not find that there had been a doping offence.

In 1999, CAS readdressed the concept of a "grey zone" in nandrolone testing. In the case of long distance swimmers Meca-Medina and Majcen[18] the CAS Panel clarified the situation stating that no such "grey zone" exists and relied instead on the 2 ng/mL threshold. This position was later affirmed the following year in the case of Alexander Leipold,[19] who was stripped of the gold medal in freestyle wrestling at the 2000 Sydney Summer Olympic Games for testing positive for nandrolone. One of the many challenges that Leipold made against his positive result was that the 2 ng/mL threshold was not reliable since endogenous production of nandrolone metabolites could exceed this level.

The CAS Panel did not accept his arguments. The situation had changed significantly since the earlier cases which discussed the "grey zone". The 2 ng/mL threshold for nandrolone metabolites had been incorporated into the Olympic Movement Antidoping Code (OMAC) and therefore was a rule that had to be applied by the Panel. Further, the scientific evidence had changed such that the Panel was satisfied that the 2 ng/mL threshold for 19-NA provided scientifically reliable proof of an exogenous administration of nandrolone. Published scientific studies as well as the experience of accredited laboratories supported the reliability of the 2 ng/mL threshold. Leipold's expert witness had not put forth any scientific studies that cast doubt on the reliability of the threshold, and merely put forward the view that there had not been sufficient study to eliminate the possibility that concentrations of endogenously produced 19-NA could exceed 2 ng/mL. The Panel found that this was not sufficient to show that the threshold was not scientifically reliable. However, the Panel did express some concerns that the evidence in support of the reliability of the threshold could be stronger. Nevertheless, they explained:

> [T]he Panel acknowledges that the IOC and other sports federations face an extremely difficult task in attempting to keep pace with the imagination and resources of cheats who seek to obtain an unfair competitive advantage in the increasingly lucrative world of sport. The Panel recognises that the IOC and sports federations must enact doping control rules based upon the best available scientific information and even if this information is, at times, rather limited.[20]

The CAS Panel in *Leipold* thus recognized that anti-doping test procedures must be evaluated based on the current state of scientific knowledge, but that scientific evidence is, unfortunately, not always foolproof.

The threshold for nandrolone remains a rule under the WADA Code. The 2006 WADA Prohibited List clearly states that an *Adverse Analytical Finding* with respect to 19-NA will be considered to be proof of exogenous origin of the metabolite. The threshold for reporting an *Adverse Analytical Finding* for 19-NA is 2 ng/mL. The original limit for women was 5 ng/mL, but this has recently been reduced and it is now 2 ng/mL as it is for men.[21]

The early inconsistencies in the CAS jurisprudence described above were caused partly by the evolution of scientific knowledge, rather than legal or jurisprudential issues imposed by the CAS. These inconsistencies were also a result of the lack of clarity in the scientific regime of the sanctioning bodies and their accompanying legal structure including the relationship between laboratory guidelines, the lists of prohibited substances and anti-doping rules.

Despite the clear acceptance by CAS of the 2 ng/mL threshold for 19-NA, athletes continue to challenge that limit. In addition to arguing that the threshold is simply unreliable, athletes have also asserted that certain factors such as intense exercise can cause temporary production of nandrolone over the allowable limit. Other athletes have made challenges alleging errors in the way that the concentration of nandrolone metabolites is reported and calculated.

i) The Exercise Induced Challenge

The issue of whether exercise can lead to production of endogenous nandrolone has been controversial. Some studies have suggested that exercise has no effect on production of endogenous 19-NA,[22] while other studies indicate that there is a very slight increase in the amount of 19-NA produced endogenously after exercise.[23] However, most of

13 *Mason v/ UCI* CAS 1998/212{"*Mason*"}; *Bouras v/* IJF CAS 1998/214 {"*Bouras*"}; *Bernhard*, supra note 3.

14 *Mason*, supra note 14.

15 *Bouras*, supra note 14.

16 *Bernhard*, supra note 3.

17 *Ibid.* at para. 8.

18 *Meca-Medina and Igor Majcen* v/*FINA* TAS 1999/A/234 and 235.

19 *Leipold v/ IOC* CAS 2000/A/310 {"*Leipold*"}.

20 *Ibid.* at para. 81.

21 These limits with respect to an *Adverse Analytical Finding* for 19-NA are set out in WADA Technical Document TD2004NA, *supra* note 4. The change to the limit for 19-NA in females occurred in August 2004, the effective date of the Technical Document.

22 Schmitt N, Flament MM, Goubault C, Legros P, Grenier-Loustalot MF, Denjean A. "Nandrolone excretion is not increased by exhaustive exercise in trained athletes" (2002) 34 Med Sci Sports Exerc. 1436-9.

23 Robinson N, Taroni F, Saugy M, Ayotte C, Mangin P, Dvorak J. "Detection of nandrolone metabolites in urine after a football game in professional and amateur players: a Bayesian comparison" (2001) 122 Forensic Sci Int. 130-5.

the studies indicate that the production of 19-NA arising from exercise is minimal and falls well below the 2 ng/mL threshold. The only studies that have demonstrated 19-NA levels generated by exercise that are higher than the 2 ng/mL threshold suffer from a fatal flaw: they do not confirm that the subjects are not administering exogenous nandrolone, either intentionally or unintentionally.[24]

In his defence, Djamel Bouras[25] asserted that the 2 ng/mL limit for nandrolone metabolites could be exceeded by endogenous production due to exercise at a time when the "grey zone" was still acknowledged and the threshold was still on shaky ground. However, even at this early stage in the jurisprudence regarding nandrolone, the CAS Panel accepted evidence that stress, dehydration, and physical effort could not have a significant influence on the endogenous production of 19-NA and could not lead to a concentration of 19-NA greater than 1 ng/mL. The CAS has continued to maintain this approach to allegations of exercise-induced production of nandrolone.

In the case of Costa Rican swimmer Claudia Poll,[26] Poll claimed that the determination of a 7 ng/mL concentration of 19-NA in her urine could have been caused by exercise, and that the threshold of 5 ng/mL (at the time) was too low.[27] The CAS Panel rejected her arguments, finding that scientific research had established that exercise could not lead to a concentration of 19-NA over the allowable limit. Furthermore, the threshold for reporting nandrolone positives for females was scientifically backed by the majority of medical opinions which stated that "stress and physical exertion has no impact on the quantity of the substance".[28] In rejecting Poll's argument the panel relied on expert testimony indicating that the 5 ng/mL limit was in fact very cautious and substantially higher than the concentration of 19-NA known to occur in non-pregnant females. The legal challenge was answered by the analysis of the scientific literature presented in evidence and evaluated by the CAS Panel. This process reflected the time tested legal technique of weighing the evidence before the adjudicators and making a judgement. The CAS has demonstrated through the decisions of its panels that it is able to address such challenges.

ii) Calculation Challenges

While some athletes challenged the validity of the 2 ng/mL limit, others challenged the accuracy of reporting and the calculations involved in determining whether their sample exceeded the threshold limit. As with all scientific measurements, there is a range of uncertainty in the calculated concentration of 19-NA in an athlete's urine sample. To establish a doping offence, it is reasonable that a sanctioning body must show not only that the concentration of 19-NA in the urine sample is greater than the limit, but also that the range of uncertainty of the concentration falls entirely above the 2 ng/mL threshold. In the *Poll* case, Poll challenged the way in which the analyzing lab had reported the range of uncertainty of the concentration of 19-NA in her urine sample. She argued that the way in which the uncertainty was reported did not comply with the rules set out by the International Organisation for Standardisation (ISO). The Panel found that even though a WADA draft document recommended using an expanded range of uncertainty, the way the uncertainty was in fact reported did not violate the ISO rules and that in any case, the range of uncertainty was well above the threshold limit regardless of the way in which it was calculated. Importantly, the Panel made it clear that it was not bound to apply the ISO standards, rather, it was bound to apply the FINA rules and to ensure that the analysis was done properly. The Panel noted that the CAS relies on the accreditation process of the labs and does not have the authority to intervene or impose its views on what it believes are appropriate laboratory procedures to be applied by these accredited labs.

The above challenge is a variation on the earlier theme that the structure of the testing rules that form the backdrop to the legal regime lacked precision and clarity. The CAS panel applied a purposive approach to the interpretation of the documentation to conclude that the laboratory was working within the prescribed parameters.

Fundamental to the maintenance of a respected adjudication process and the integrity of the jurisprudence arising therefrom is a profound need to conduct a careful and meticulous review of scientific data, journal articles and expert testimony. The CAS has been on the whole vigilant in its conduct and review of scientific data, articles and expert testimony despite diversity of view within the scientific community on some matters. Such vigilance is essential for the continuing success of the CAS. The error committed by the IAAF Doping Review Board (which conducted doping arbitrations at the time) in the Merlene Ottey case is illustrative of the negative impact that lack of vigilance can reek upon an organization.[29]

Another case illustrating the importance of accuracy when reporting the detection of nandrolone is the case of British triathlete Spencer Smith,[30] who tested positive for nandrolone in the 1998 Hawaiian Ironman. At one point in the hearing the anti-doping lab director stated that an error had recently been discovered, and that the reported concentration of 19-NE should have been 3 ng/mL instead of 8 ng/mL. Due to this discrepancy between the results that were initially reported and the corrected results, the CAS Panel did not find that Smith had committed a doping offence. The Panel stated that when doubt has been raised with respect to a testing procedure, the benefit of that doubt must go to the suspected athlete.

Despite what occurred in the Spencer Smith case, the rules of most IFs and the WADA Code provide that minor irregularities in sampling, custodial, and testing procedures will not normally invalidate a finding of a doping offence. In the case of Czech tennis player Petr Korda,[31] the athlete attempted to defend himself against a charge of nandrolone doping by relying on several minor deviations from the established procedures for sampling and testing. The Panel applied Section U of the ITF rules at the time, which stated that any deviations from anti-doping control procedures do not invalidate the finding, procedure, decision, or positive test result, unless that deviation raises a material doubt as to the reliability of the finding, procedure, decision or positive test result.[32]

b) Ingestion Without Intention Challenges

i) Contaminated Supplements

At the turn of the millennium there seemed to emerge a large number of cases in which athletes tested positive for nandrolone. Athletes blamed their positive results on ingesting nandrolone unintentionally through contaminated or unlabelled dietary supplements or through foods that contained nandrolone.[33]

Contaminated supplements can occur either through deliberate or

24 See the *Nandrolone Progress Report* to UK Sport Council from the Expert Committee on Nandrolone chaired by Dr. Vivian James (February, 2003) at paras. 13-22. Available at www.uksport.gov.uk.

25 *Bouras*, supra note 14.

26 *Poll v/FINA* CAS 2002/A/399 {"*Poll*"}.

27 This threshold limit came from a subcommittee of the IOC Medical Commission who produced a document for the guidance of accredited laboratories: *Analytical Criteria for Reporting Low Concentrations of Anabolic Steroids (August 1998).* It can be found as an appendix to *Nandrolone Review* a report to UK Sport in January of 2000. See www.uksport.gov.uk.

28 *Poll*, supra note 27 at para. 51.

29 In the decision dated 7 July 2000, the Doping Review Board accepted expert testimony that incorrectly took account of dehydration causing Merlene Ottey's urine sample to be concentrated. To account for such circumstances when the specific gravity of an athlete's urine sample is greater that 1.02, a correction factor is applied to the threshold limit in order to compensate for the concentration of the urine. This has the effect of raising the thresholds over which a positive analytical result will be reported by the analyzing laboratory. What the Review Board did was to apply the correction factor to lower the results of the analysis resulting in the reading being apparently below threshold for women. The Review Board had been misled in its deliberations by an expert providing the incorrect calculation method. The disrepute this brought upon the IAAF may have been one of the contributing factors leading the IAAF in Edmonton, Alberta in 2001 to agree to join the CAS system and refer doping arbitrations to CAS.

30 *USA Triathlon v/ Spencer Smith* (CAS, Lausanne, 31 May 2000).

31 *ITF v/ Korda*, CAS 99/A/223.

32 A similar provision is found in article 3.2.2 of the WADA Code, which states that departures from International Standards that do not cause an Adverse Analytical Finding will not invalidate the results. However, if an athlete is successful in establishing that a departure occurred, the sanctioning body bears the burden of proving that the departure did not cause the Adverse Analytical Finding.

33 *Kicker Vencill v/ USADA*, CAS 2003/A/484 {"*Vencill*"}.

accidental mislabelling of products or the accidental mixing of ingredients by manufacturers in the course of producing a supplement. Such potential problems have been greatly intensified by greater access to the Internet which has facilitated both knowledge and access to supplements and their purchase by people worldwide. The extent of the problem was dramatically illustrated by an 2002 IOC study of 634 non-hormonal dietary supplements from 13 countries.[34] Ninety-four (14.8%) of the tested supplements were found to contain prohibited anabolic-androgenic steroids not listed on any label. From at least that date, or possibly even earlier, athletes have been warned about the risks associated with taking dietary supplements. Despite these warnings however, the CAS jurisprudence is rife with examples of athletes who have taken a supplement that has resulted in an adverse analytical finding.[35] Though the problem has been alleviated somewhat by legislation regarding supplements introduced by the United States government,[36] the problem continues.[37] However, it has now shifted away from nandrolone to steroids that are undetectable in standard laboratory screening procedures. The challenge for the testing labs to keep up with the substance manufacturers is obvious. The question is, how does the CAS deal with this challenge?

Both the WADA Code, and the variations adopted by many international federations provide for strict liability with regard to doping infractions, such that the mere presence of a prohibited substance in the athlete's body is considered to be a doping offence, even if the substance was ingested unintentionally. As a result of this strict liability, an athlete who ingests nandrolone unintentionally will still be deemed to have committed a doping offence. However, if the athlete can establish that the ingestion of a prohibited substance such as nandrolone was unintentional, then it is possible that there could be a reduction in the sanction they receive.[38] In such cases, CAS must determine whether or not nandrolone entered the athlete's body in the way claimed by the athlete, and whether the athlete should bear some responsibility for the inadvertent ingestion.

ii) Other Claims of Ingestion

One potential source for the unintentional ingestion of nandrolone is its possible presence in the organs of certain animals that might then be eaten by humans. This concern is best illustrated by the case of *Meca-Medina and Majcen v/ FINA*.[39] Meca-Medina and Majcen both tested positive for nandrolone at the same event, and claimed that their positive results were due to the consumption of a certain dish served at the hotel where they were staying. They claimed that this dish, called "Sarapatel" contained uncastrated boar offal and that consumption of this meat led to their positive test results. As a result of strict liability, the athletes bore the burden of proving that the nandrolone in their bodies was due to the consumption of this dish. A scientific study had been performed where it was observed that consumption of uncastrated boar meat could indeed lead to the presence of nandrolone metabolites that exceeded the allowable limits for a certain time period. Despite the new scientific findings, the athletes were still unsuccessful in establishing that the nandrolone metabolites in their samples were the result of the consumption of boar meat. The evidence and the nandrolone test results were not sufficiently consistent with this explanation, even if it were theoretically possible.

Scientific research has continued to support the notion that the organs of certain animal species could lead to a positive finding for 19-NA.[40] But other athletes such as Myriam Léonie Mani[41] who have relied on this defence have not been successful. Part of the reason for this is that the Nandrolone Progress Report to the U.K. Sports Council now advises athletes that it recommends that boar and horse meat be avoided.[42] The WADA Code, and most other doping rules, place a high degree of responsibility on the athlete for what they consume. The known prevalence of nandrolone contamination in dietary supplements as well as certain specified foods should make an athlete wary of taking supplements that have not been properly assessed for the presence of contaminants and of eating certain types of meat. Accordingly, panels may decide not to reduce the sanction of an athlete or to reduce it only minimally because the athlete should have taken more precautions. The case law seems to support this proposition. For example, U.S. swimmer Kicker Vencill[43] was unsuccessful in obtaining a reduction of his suspension for unintentionally taking nandrolone through unlabelled dietary supplements.

The jurisprudence involving contaminated supplements or food products relies upon the principle of strict liability to place a burden of proof by explanation on the athlete. That obligation is an onerous and expensive one to undertake. There is only one CAS case,[44] of which I am aware, that has resulted in an exoneration as a result of a discharge of the burden of proof. The legal technique of strict liability is the core reason for this being the case.

iii) Unexplained Challenges

The most difficult issue that has arisen with respect to nandrolone contamination is the eight ATP tennis players that tested positive for nandrolone within a period of 11 months between August 2002 and July 2003.[45] While these cases did not reach the CAS level, it demonstrates the difficulties that can arise in nandrolone testing. All of these athletes had concentrations of nandrolone metabolites that were consistent with the contamination of dietary supplements. Importantly, analysis of these samples revealed that they all shared a distinct signature, suggesting a common source. The ATP had been supplying the athletes with electrolyte tablets, and the circumstantial evidence known and available at the time indicated that these tablets were the likely source of the positive nandrolone tests.

While normally athletes are guilty of a doping offence no matter what the reason for the presence of a prohibited substance in their system, in this case, at the time of the hearing there was evidence that the sanctioning body (the ATP) had been responsible for the unintentional ingestion of nandrolone by the athletes. As a result, the independent doping tribunals that heard these cases applied the principle of equitable estoppel, preventing the ATP from obtaining the benefit of its strict liability rules because they had been the likely agent responsible for their breach. The ATP could offer no other evidence to establish intention or that a doping offense had occurred. Thus, the allegations of a doping offence remained unsubstantiated and the athletes were exonerated because the cases had not been proven. Further scientific investigation after the cases had been processed later revealed that the electrolyte tablets in question were not in fact contaminated with nandrolone. Furthermore, even after the ATP had

34 See the discussion of the study and other ones in the *Nandrolone Progress Report* to UK Sport Council from the Expert Committee on Nandrolone (February, 2003) at p. 5 paragraph 4 and subsequent.

35 *Leipold*, supra note 20; *Aanes v/ FILA*, CAS 2000/A/317; *Demetis v/ FINA* CAS 2002/A/432; *Vencill, supra* note 34; *IAAF v/ ÖLV & Elmar Lichtenegger*, CAS 2004/A/624; *Guest v/ CGC & TC*, CAS C.G. 02/001; *Knauss v/ FIS*, CAS 2005/A/847.

36 For a long time prohormones such as 19-norandrostenedione and androgestinedione could be sold as dietary supplements, however, the implementation of the *The Anabolic Steroid Control Act* of 2004 has made distributing and possessing these types of compounds illegal under U.S. federal law.

37 The UCLA accredited laboratory at the request of the Washington Post tested five dietary supplements in 2005. Four contained steroids that were previously undetectable and the other contained THG, only recently discovered during the BALCO scandal. See: Amy Shipley "Chemists Stay a Step Ahead of Drug Testers" *The Washington Post* (18 October 2005), E01, online: http://www.washingtonpost.com/wp-dyn/content/article/2005/10/17/AR2005101701622.html.

38 See the WADA Code provisions on reduction in sanctions for no fault or negligence or no significant fault or negligence at article 10.5. See Richard McLaren, "Exceptional Circumstances: Is it Strict?" (2005) 5 I.S.L.R. 32 (Sweet & Maxwell, London).

39 CAS 99/A/234 and 235; CAS 2000/A/270.

40 De Wasch K, Le Bizec B, De Brabander H, Andre F, Impens S. "Consequence of boar edible tissue consumption on urinary profiles of nandrolone metabolites. II. Identification and quantification of 19-norsteroids responsible for 19-norandrosterone and 19-noretiocholanolone excretion in human urine." (2001) 15 Rapid Communications in Mass Spectrometry. 1442-1447.

41 *IAAF v/ CMR & Mani*, CAS 2003/A/448.

42 *Nandrolone Progress Report* to UK Sport Council from the Expert Committee on Nandrolone (February, 2003).

43 *Vencill, supra* note 34.

44 *French v/ Australian Sports Commission and Cycling Australia* CAS 2004/A/651 issued 11 July 2005.

stopped distributing supplements, many tennis players continued to exhibit low levels of nandrolone when tested, and these samples continued to have the same unique signature. This controversy has still not been resolved, but recent discoveries relating to nandrolone testing might possibly provide some explanation.

c) The Challenge of Changing Scientific Knowledge

The challenge that changing scientific knowledge has presented in nandrolone testing is demonstrated by the case of the New Zealand swimmer Trent Bray.[46] Bray's A and B samples showed concentrations of 19-NA at 4 and 3.5 ng/mL, respectively. Bray complained that the positive result was due to the fact that his urine sample had been held up in customs and was thus in transit for two weeks during the summer. Bray claimed that the urine samples stored at high temperature for such a period of time could undergo degradation and bacterial activity. The Panel did not accept Bray's arguments, as the urine sample appeared normal when it finally arrived at the laboratory. Further, the Panel did not accept that degradation or bacterial activity could lead to the formation of nandrolone metabolites. Bray attempted to show that 19-NA could be formed in the sample through the transformation of endogenous hormones such as testosterone or androsterone into 19-NA. However, Bray's expert witnesses were only able to show that such a transformation was a theoretical possibility. There was no scientific evidence suggesting that such a transformation did actually occur. The Panel stated:

> Careful evaluation of the evidence before it has led the Panel to the conclusion that a pathway from testosterone or androsterone to 19-norandrosterone outside the human body may be theoretically conceivable but that absent any scientific evidence to this effect it remains pure speculation on which the Panel is unwilling to base its decision.[47]

In the result, Bray was found to have committed a doping offence and received a suspension of two years. However, while the chemical pathways put forward in Bray's defence were at the time merely theoretical, scientific knowledge has advanced since then.

Recent scientific studies have resulted in the discovery of a phenomenon described as *active* or *unstable* urine that could potentially affect the results of nandrolone testing.[48] It is possible for a urine sample to incubate its own metabolites of nandrolone (though it is rare and only occurs under certain conditions). WADA has taken steps to understand and recognize this phenomenon and they have modified their testing procedures in order to detect it and to eliminate the possibility of false positives.[49] While the recent discoveries and the modifications to the testing protocol have not yet been the subject of a CAS ruling, these issues will no doubt be raised in future cases involving positive tests for nandrolone.

The research has revealed that in certain rare circumstances, a chemical reaction can occur in the bottle after a urine sample has been provided, whereby two endogenous hormones, androsterone (A) and etiocholanolone (E), are converted into 19-NA and 19-NE, metabolites of nandrolone that are tested for in doping analysis. Urine samples that exhibit this phenomenon, known as "unstable urine", exhibit certain unique characteristics. These samples exhibit cloudiness and are highly concentrated, and high temperature appears to be a factor in the chemical reaction. Furthermore, the phenomenon tends to occur when the ratios of the amount of A, E, 19-NA, and 19-NE found in the sample meet certain criteria. To date, the research indicates that the highest concentration of 19-NA that has been recorded as a result of the phenomenon is 5.4 ng/mL.[50]

While WADA has maintained the 2 ng/mL limit for the presence of 19-NA in an athlete's urine sample, they have modified the testing procedures for samples that fall within a range of 2 to 10 ng/mL. First, a urine sample that produces a result in this range must exhibit the known characteristics of unstable urine; otherwise, the result will be considered positive for nandrolone. If a urine sample does exhibit the characteristics of unstable urine, a "stability" test will be performed. In essence, the stability test is a method of determining whether the chemical reaction that constitutes the phenomenon of unstable urine can be demonstrated to occur in the athlete's urine sample.

CAS has not yet knowingly dealt with an unstable urine case. When it does, the legal requirements used previously to assess the acceptance of the variation in the testing procedure amongst the scientific community will be examined and weighed to come to the appropriate legal conclusions. This legal technique of weighing the evidence before the adjudicators and making a judgement is well understood and can be seen to be operating in many doping cases. These developments should present no new challenges from the point of view of CAS.

While the WADA modification to the nandrolone testing procedure may prevent the "unstable urine" problem from causing false positives in the future, there may be little that can be done about cases in the past. In many cases, there may no longer be any urine samples that are available in order to test for the "unstable urine" phenomenon. It is possible that several "borderline" cases in the past, such as the tennis cases discussed above, may actually have been examples of unstable urine.

d) Summary

The assessment of a doping infraction is always based upon the scientific knowledge of the day. The foregoing review of the testing procedures for nandrolone as a prohibited substance clearly reveals that the ever expanding boundaries of scientific knowledge can ultimately call into question a result that was accepted as hard fact only years or months before. Some years ago it was thought that nandrolone did not occur naturally in the body. Later, it was recognized that it occurred naturally in pregnant women and in small quantities in men. Consequently, thresholds were introduced to accommodate this change in scientific knowledge. Today, those thresholds have been modified to a unisex level with a special procedure to account for the possibility of concentrated urine or active, unstable urine that may incubate its own nandrolone in the bottle. The CAS has not yet reviewed all of these challenges to the nandrolone testing procedure. To the extent that they have, none have so far resulted in legal obstacles being placed in the way of the development of revisions to the procedure. The concern must then be that in light of these developments, some athletes may well -if tested today- be found not to have produced an adverse analytical result based on the evolution of scientific understanding related to testing for the substance. They are the victims of the changing state of scientific knowledge. At least in the sport of men's professional tennis, the adjudication system protected some of the athletes by the estoppel applied to the strict liability regime.

2. Erythropoietin

The naturally occurring protein hormone erythropoietin (EPO) is produced by the kidney and causes the production of new red blood cells (erythropoiesis).[51] The function of EPO is to stimulate the bone marrow to produce more red blood cells, which carry oxygen throughout the body. An increased amount of red blood cells can be extremely beneficial to all athletes, but particularly endurance athletes, because it provides for uptake of greater amounts of oxygen, allowing athletes to increase their level of exertion and to maintain that level for longer periods.

Using genetic engineering, artificial forms of EPO have been devel-

45 See ATP Press Release "ATP Expands its Efforts to Determine Cause of Low-Level Nandrolone in Test Results", March 10, 2004, online: http://www.atptennis.com/en/antidoping/nandrolone_release.pdf; See also "WADA Report on ATP Cases", July 2004, online: http://www.wada-ama.org/rtecontent/document/wada_atp_report.pdf.

46 *Bray v/ FINA*, CAS 2001/A/337.

47 *Ibid.* at para. 49.

48 Thieme, D., Anielski, P., Grosse, J., Hemmersbach, P., Lund, H., Rautenberg, C., "Kinetic of in-situ demethylation of deuterated endogenous steroids in urine samples" In: W. Schänzer, H. Geyer, A. Gotzmann, U. Mareck (eds.) Recent advances in doping analysis. Sport und Buch Strauß, Köln (2004) 177-188.

49 Explanatory Note, *supra* note 5.

50 *Ibid.*

51 Françoise Lasne and Jacques de Ceaurriz, "Recombinant erythropoietin in urine", (2000) 405 Nature 635.

oped that have typically been used to treat diseases such as anemia caused by renal failure. Both the natural and synthetic forms of EPO effectively stimulate the production of red blood cells. As a result, many athletes are turning to the administration of artificial EPO as a means of enhancing their performance, which constitutes a doping offence under the WADA Code.[52] Synthetic EPO exists in several forms. The first type of artificial EPO to be developed was known as recombinant EPO, {rEPO}, and is produced by splicing the human EPO gene into cultured animal cells. More recently, another form of artificial EPO called darbepoietin has been developed using a similar process, but differing in that it involves an EPO gene sequence that has been specially engineered. The naturally produced version of EPO is sometimes referred to as endogenous EPO or urinary erythropoietin (u-EPO).

The human body does not naturally produce rEPO or darbepoietin, and its presence in the body of an athlete is therefore indicative of the intentional administration of an external substance.[53] The challenge for the WADA accredited laboratories has been to find a test procedure that identifies artificial EPO and validly and reliably distinguishes it from endogenous EPO. As the testing procedures for EPO have evolved, the CAS continues to hear new challenges to EPO analytical positive results. In hearing these challenges, the CAS has had the opportunity to consider the scientific and legal standards that must be met by a new testing procedure. By reviewing the history of the EPO test in the context of the CAS jurisprudence, any limitations that have been imposed on the use of the testing procedure for legal purposes can be examined to determine if the test is acceptable to establish a doping offence.

a) The Original Direct Urine Test

The direct urine test for rEPO was first introduced at the Olympic Games in Sydney, Australia in 2000 and was used in combination with an indirect blood test for rEPO.[54] The indirect blood test was conducted first, but could not conclusively prove use of rEPO on its own. If the indirect blood test suggested possible use of rEPO, then the direct urine test - which directly indicates the presence of r-EPO in the urine - is used.[55] The laboratory procedures for carrying out the analysis were first introduced just prior to the Sydney Games and have gone through a number of refinements since that time.

Since only the direct urine test is used as definitive proof of the presence of rEPO, most of the scientific challenges to the EPO testing procedures heard by CAS have focused upon it. The direct urine test distinguishes between endogenous EPO and artificial EPO based on differences in the complex sugar chains that make up a significant part of an EPO molecule. Even though rEPO is produced using the natural human gene for EPO, the production of rEPO in animal cells as opposed to human cells causes rEPO molecules to exhibit differences which cause them to have different electrical charges. The direct urine test distinguishes between rEPO and endogenous EPO based upon the difference in charge.[56]

After some preparatory steps, the urine sample is run through a gel in which a pH gradient has been set up by running an electrical current through it. Depending on the charge on a molecule, it will move to a different location on the gel, allowing for the separation of different forms of EPO molecules. Afterwards, all of the different forms of EPO molecules (both endogenous and artificial) are visualized using an antibody that recognizes EPO. Eventually, an image called an electropherogram is produced, showing the different forms of EPO (also called isoforms) present in a urine sample.[57] Endogenous EPO consists of many different isoforms that occupy the central region of an electropherogram, in between the acidic and basic regions. In contrast, rEPO consists of only five isoforms that occupy the basic range of the electropherogram.

Though there can be some overlap between the endogenous EPO isoforms and the rEPO isoforms on an electropherogram, it is usually quite clear from observing an electropherogram whether rEPO is present in a urine sample. In order to deal with the fact that endogenous EPO isoforms could overlap with rEPO isoforms, certain criteria for interpreting the electropherograms were developed. These criteria were designed such that, by using them, the risk of false positives would be negligible. Many of the initial scientific challenges to the EPO testing procedure heard by CAS involved these interpretation criteria.

The first cases adjudicated around the world did not arise until 2001. The jurisprudential basis for the acceptance of rEPO testing began with the Court of Arbitration for Sport {CAS} decision in *Meier* v. *Swiss Cycling*.[58] That case arose in the era when each international sports federation made its own rules about doping in contrast to the harmonized rules of WADA, which established international standards for testing. In the *Meier* case, the CAS Panel accepted that the *direct urine test*, as it was then referred to, was reliable and might be applied to distinguish endogenous EPO from exogenous EPO producing an adverse analytical result.[59]

Following the *Meier* decision the next case, *UCI v. Hamburger*,[60] CAS challenged not the general reliability of the test but whether there was a laboratory standard of 80% basic area isoforms percentage {BAP}. This interpretation technique involved a visual and quantification test to interpret the electropherogram.[61] The Panel in *Hamburger* found that the international federation did not have to follow the IOC practice of requiring an 80% BAP in its own anti-doping rules. However, the evidence was that the laboratory doing the testing followed the practice in any event. The Panel held that in so doing it must apply the 80% BAP method of interpretation to both the "A" and "B" sample and that it had not done so. Therefore, no doping infraction had occurred because, according to the criteria used at the time by the laboratory, the "B" sample did not confirm the "A" sample.

The EPO test procedure appeared to be on a slippery slope in the CAS jurisprudence given that *Meier* had been found to have committed a doping offense and *Hamburger* had not. These decisions reflect the parallel developments in the earlier CAS jurisprudence on nandrolone being influenced by changing understandings of the science and its interpretation. The early inconsistencies in the CAS EPO jurisprudence were caused by the lack of clarity in the scientific regime

52 As an aside in October of 2005 American champion skier Bode Miller was quoted in the newspapers as saying the sporting playing field cannot and should not be made level, Miller said. "Nothing's equal," Miller said. "If you want to make it equal, then make everything legal. So you can do whatever the hell you want."

53 See Françoise Lasne, *et al.*, "Detection of Isoelectric Profiles of Erythropoietin in Urine: Differentiation of Natural and Administered Recombinant Hormones" (2002) 311 Analytical Biochemistry 119-126 at 120 stating that ... *endogenous EPO is synthesized in the human kidney, whereas recombinant EPO is synthesized in Chinese hamster ovary cells.*

54 The indirect blood test for EPO is described in: Robin Parisotto, *et al.*, "A novel method utilising markers of altered erythropoiesis for the detection of recombinant human erythropoietin abuse in athletes" (2000) 85 Haematologica 564-572.

55 See Rymantas Kazlauskas, *et al.*, "Strategies for rhEPO Detection in Sport" (2002) 12 Clinical Journal of Sport Medicine 229-235.

56 Françoise Lanse, "Double-blotting: a solution to the problem of non-specific profiles of erythropoietin in urine: differentiation of natural and administered recombinant hormones." (2001) 253 J. Immunol Methods. 125-131.

57 Don H. Catlin,. *et al.*, "Comparison of the Isoelectric Focusing Patterns of Darbepoetin Alfa, Recombinant Human Erythropoietin, and Endogenous Erythropoietin from Human Urine" (2002) 48 Clin. Chem. 2057-2059.

58 CAS 2001/A/345 {"*Meier*"}.

59 The words of the Panel were: *This "direct method" combines an isoelectrical focussing with a double immunal blotting. The method is based on the finding that artificially produced rEPO behaves differently in an electrical field than human nEPO and can therefore be distinguished from one another. A second basic assumption of the test method is that, as is the case with many steroids, the production of natural hormones is reduced when an artificial hormone is introduced...*

60 CAS 2001/A/343 {"*Hamburger*"}.

61 The basic area percentage {"BAP"} method of interpreting the EPO test was described as follows in *IAAF v/ MAR and Boulami* CAS 2003/A/383: *[O]ne of the 100% r-EPO control samples is used to establish a horizontal dividing line ... drawn at the bottom of the most acidic rung of the 100% r-EPO sample. ... The EPO ladder of the athlete urine sample in question is then examined relative to the horizontal baseline. ... [A] machine then measures what percentage of the surface area of these rungs appears above the horizontal baseline in the basic area of the gel.* This percentage figure is the BAP. It is one of several methods of interpreting the electropherograms although in the early testing days it was the predominant method.

and its accompanying legal structure through the prohibited list of a particular sports federation. The lack of precision in the jurisprudence was not the result of legal or jurisprudential issues imposed by the CAS.

b) The Refinement of the BAP Test Interpretation Criteria

The next step in acceptance of the rEPO testing methodology came in the case of Moroccan steeplechaser Brahim Boulami[62] who disputed the validity of the test based on the BAP (80%) guideline that had been previously used to establish the presence of rEPO. He argued that the percentage of basic isoforms in endogenous EPO were higher than previously thought. Boulami also argued that the rEPO test had not been internationally accepted or validated by the scientific community, did not fulfil standard requirements, and that the laboratory was not properly accredited to perform the test.

In rejecting Boulami's arguments the CAS Panel found the test to be reliable and internationally accepted for the purpose it served. The percentage of basic isoforms in endogenous EPO was not higher than previously thought among the general population. As such, the respondent failed to cast doubt on the proposition that the 80% cutoff was reasonable and largely eliminated the risk of false positives in urinary rEPO tests.

Boulami's argument that the rEPO test had not been internationally accepted or validated by the scientific community was also rejected. The test was accepted by all previous CAS Panels. The Panel accepted the evidence that the risk of false positive at the 80% BAP cutoff was extremely low. Boulami's final argument based on the laboratory's lack of specific accreditation to conduct the rEPO test was not accepted by the CAS Panel. However, the Panel did find that the lack of accreditation for the specific test meant that the IAAF had the burden of proving that the test was conducted in accordance with the scientific community's practices and procedures and that the testing lab had satisfied itself of the validity of the test before using it. The Panel stated that this burden-shifting rule "provides the necessary balance between the needs of IOC laboratories to implement new, reliable testing methods as quickly as possible, on the one hand, and the interests of athletes and the sporting community in ensuring trustworthy test results, on the other."[63]

The *Boulami* case represented a new departure in the jurisprudence in that the purposive approach to interpretation of the rules and framework was articulated. It involved undertaking an analysis of the scientific literature presented in evidence and evaluated by the CAS Panel with a view to balancing the competing interests of the various constituent needs. This process reflects the time tested legal technique of weighing the evidence before the adjudicators and making a judgement. Once again the CAS proved to be quite able at dealing with such challenges.

Following the *Boulami* case, the next development in the acceptance of the EPO testing procedure came in *USADA* v. *Sbeih*.[64] Sbeih claimed that the 80% BAP threshold was not an appropriate criterion to determine a positive result for rEPO. The CAS Panel thoroughly rejected this argument, citing previous CAS cases where the 80% BAP threshold had been accepted. Also, another scientific study was available indicating that at 80% BAP, the risk of false positive is actually 1 in 500,000 as opposed to the 1 in 3,161 figure that had been stated in *Boulami*. Furthermore, evidence was presented that technology had advanced such that a threshold below 80% BAP might be used without risking the possibility of a false positive. Interestingly, other more recently developed criteria that could be used to determine the presence of rEPO instead of 80% BAP were described in the *Sbeih* case. Sbeih's EPO test was also positive for rEPO according to these other criteria.

The *Sbeih* case was a further illustration of the analysis of the scientific literature presented in evidence and evaluated by the CAS Panel. It also provided the foundation for the eventual elimination of the BAP as an interpretation criterion in EPO testing.

c) The Elimination of the BAP Criterion

The use of criteria other than 80% BAP to determine a positive result for rEPO first came about in early 2005 in *USADA v. Bergman*.[65] Bergman was an American cyclist who was found to have tested positive for rEPO. Despite the fact that both his "A" and "B" samples had BAP's just below 80%, USADA charged him with a doping offence, which Bergman appealed to CAS. Bergman argued that 80% BAP was a standard threshold and that BAP values below this level could not be proof of a doping offence. The CAS Panel held that the UCI anti-doping rules allowed USADA to prove the doping offence "by any means" and that the CAS had never ruled that the 80% BAP threshold was absolutely required in order to prove the presence of rEPO in a urine sample.

The Panel was comfortably satisfied that new scientific findings established that the presence of rEPO could be proven even with BAP values less than 80%. The Panel relied on recent research that demonstrated that the risk of false positives at 80% BAP had been much lower than was originally thought. Criteria other than the BAP could also be relied upon when the BAP is below 80%. Bergman's sample was positive according to these other criteria, including the new WADA criterion for EPO testing described in Technical Document TD2004EPO, entitled: *Harmonization of the Method for the Identification of Epoetin Alfa and Beta (EPO) and Darbepoietin Alfa (NESP) by IEF-Double Blotting and Chemiluminescent Detection.* The new WADA criterion was not yet in force at the time of Bergman's positive result, but was evidence that further supported the Panel's finding that a doping offence had been committed.

Dovetailing and building upon previous jurisprudence can be seen in the *Bergman* case, despite the lack of precedent in arbitration. The CAS Panel weighed and evaluated the case before it, but was mindful that some of the ground it was covering was not new. It determined that its role in the balancing of interests, spoken of in the *Boulami* case, required it to be satisfied that the risk of a false positive for an athlete was at an acceptably low level to establish the doping offence.

d) The Most Recent Version of the EPO Test Procedure

The demise of the BAP criteria arose at the outset of 2005. The new WADA criterion for determining the presence of rEPO described in the technical document TD2004EPO came into force as the relevant international standard for interpreting the electropherogram.[66] That document sets out three identification criteria for rEPO. It also states that: "*Further research and experience has indicated than the identification criteria below are more discriminating than the "80% basic bands" rule..."* and that the 80% BAP threshold should no longer be used.

The testing procedure for the detection of EPO has been under scrutiny in each phase of its refinement over the four years it has been the subject of review by CAS. The most recent phase, discussed above, will also likely gain acceptance by CAS as the *obiter dicta* in *Bergman* would suggest. However, we will have to await developments in this area to assess whether the CAS jurisprudence will be a barrier to the evolution of science and the refinement of the testing procedure for rEPO.

e) The Active and Effort Urine Refinement to the Test Procedure

To date, most of the CAS jurisprudence regarding EPO testing has focused on the interpretation of the electropherogram and the fact that endogenous EPO isoforms might overlap with rEPO isoforms. However, the most significant threat to the acceptance of the EPO testing procedures has arisen through the recognition of certain rare phenomena that can cause alterations to the profile of endogenous EPO isoforms.

The first such phenomenon to be recognized is known as "active urine". The "active urine" phenomenon does not normally occur during EPO testing. However, in rare circumstances it may occur in par-

62 *IAAF v/ Boulami* CAS 2003/A/452 {"*Boulami*"}.
63 *Ibid.* at para. 5.49.
64 *NACAS* AAA No. 30 190 001100 03 {"*Sbeih*"}.
65 CAS 2004/O/679 {"*Bergman*"}
66 See WADA Technical Document TD2004EPO, entitled: *Harmonization of the Method for the Identification of Epoetin Alfa and Beta (EPO) and Darbepoietin Alfa (NESP) by IEF-Double Blotting and Chemiluminescent Detection* {"WADA TD2004EPO"}.

ticular individual urine samples. The phenomenon may be the result of multiple factors such as storage at high temperature, enzymatic activity, or bacterial contamination.[67] These factors may act to degrade EPO molecules, causing isoforms to be eliminated or to move to locations on an electropherogram that are different from their normal location.

The "active urine" phenomenon was first recognized in the summer of 2003, and the first publicized example of the "active urine" phenomenon occurred in the case of Bernard Lagat,[68] a Kenyan middle distance runner. Lagat's "A" sample tested positive for EPO just prior to the 2003 World Championships in Paris, forcing him to withdraw from the competition. About a month later, testing of Lagat's "B" sample revealed that his urine sample exhibited the active urine phenomenon, leading to his exoneration. The newly introduced "activity test" that had been implemented by the laboratory indicated that urine "activity" was indeed taking place.[69]

There has been little discussion of the active urine phenomenon or the activity test in the CAS jurisprudence so far. The activity test was mentioned with only minor comment in the *Sbeih* case; however, the Panel recommended that information concerning the activity test be provided to the athlete as part of the laboratory packet. Currently, the details of the activity test are spelled out in WADA Technical Document TD2004EPO.[70] The stability test that is performed to test for the "active urine" phenomenon is in many ways analogous to some of the new testing procedures that have been implemented to deal with the "active urine" phenomenon that has been observed in nandrolone testing.

It is likely that the stability test and its effectiveness in dealing with the "active urine" phenomenon will be subject to more intensive scrutiny in future CAS jurisprudence. If this aspect of the EPO testing procedure is challenged in the future, it may be necessary for anti-doping laboratories to provide evidence to CAS showing that the stability test is effective in preventing the "active urine" phenomenon from interfering with the results of EPO testing procedures.

The second rare phenomenon that has been recognized as altering endogenous EPO profiles is described as "effort urine". "Effort urine" has only been recognized recently, and the phenomenon is not fully understood; however, it does seem to arise on certain rare occasions, when athletes provide urine samples after particularly intensive exercise.[71] While the scientific basis of the "effort urine" phenomenon is still being examined, the phenomenon is recognized by anti-doping laboratories and can be distinguished from positive and negative test results for artificial EPO. Several WADA accredited laboratories are participating in research designed to further understand what causes the "effort urine" phenomenon.

New interpretation criteria for the EPO testing procedure have been issued to accredited laboratories in response to the "effort urine" phenomenon.[72] The new criteria have not yet been formalized into a technical document, since further research is required before the phenomenon is fully understood.

The "active urine" and "effort urine" phenomena have brought the EPO test under attack from athletes who have tested positive and claimed that these or similar phenomena have caused a false positive result in their case. These athletes are claiming that the current EPO testing procedure is unreliable and that positive results should not be declared until a new test for EPO is developed.

The most publicized EPO case has been that of Belgian triathlete Rutger Beke,[73] who has created considerable controversy in the media with respect to EPO testing.[74] Rutger Beke initially tested positive for EPO in September 2004. In March 2005, the Flemish Doping Commission suspended Beke for 18 months. However, Beke appealed the decision, and in August 2005 the Flemish Disciplinary Commission exonerated him of the doping offence. According to press reports,[75] Beke worked with scientists who showed that Beke could test positive for rEPO after intense exercise, without having taken rEPO. Since Beke's alleged false positive results occurred after intense exercise, it appears that Beke's case could have been an example of the "effort urine" phenomenon. However, the explanation of Beke's testing results provided by the scientists who worked with him appears quite complex.

The work conducted by Belgian scientists used to exonerate Rutger Beke was pre-published online in Blood Journal on February 21, 2006.[76] The article claims that after intense exercise, urine samples taken from Beke can produce a false positive caused by a substance that is not EPO. The experiments described in the article appear to demonstrate that the antibody used to identify and visualize the various isoforms of EPO also binds to other substances. The potential cross-reactivity of the EPO antibody has also been mentioned in another recent scientific article written by Khan *et al.*[77] This might cause these other substances to appear on an electropherogram and potentially be mistaken for rEPO isoforms. The Beke article further notes that the athlete suffers from proteinuria, a condition where abnormally large amounts of protein are excreted in the urine during intense exercise. The presence of extra protein in urine would make it more likely that the EPO antibody would bind to a protein unrelated to EPO. Interestingly, the association of proteinuria with intense exercise suggests a possible connection with the "effort urine" phenomenon that has been recognized by WADA.[78] However, the authors of the article also make it clear that their results do not invalidate the test for rEPO as a whole, since the possibility of any false positive risk is likely restricted to only a very few athletes who have a medical condition similar to the one exhibited by Beke. They also note that the risk of any false positive could be prevented by taking very simple steps.

The scientific evolution in knowledge and interpretation of the test procedure reveals a similar course of learning to that involving nandrolone. The CAS jurisprudence had to date been supportive in recognizing these evolutionary changes in the EPO testing procedure. It appears that CAS has not created barriers to the evolution of the science, based on the decision in *IAAF v/ Eddy Hellebuyck*.[79] The case arose out of an appeal by the IAAF of the USADA and NACAS/AAA adjudication process in which the full sanction for ineligibility was not applied. The athlete on this appeal took up the opportunity to have his case heard *de novo* as permitted under the Code of Sports Related Arbitration. All of the matters previously challenged in other cases were raised and confirmed as already decided in *Hellebuyck*. The case then went one step further and dismissed new arguments based on the one scientific article[80] used to cast doubt on the reliability of

67 See Report of Dr. Hans Heid (8 October 2003) entitled "Report of B-sample testing in the laboratory of Prof. W. Schänzer, Institute of Biochemistry, Germany, Sport University, Cologne", online: http://www.letsrun.com/2003/lagatfull.doc {"Heid Report"}.

68 "Lagat fails drugs test" *BBC Sport* (3 September 2003), online: BBC Sport http://news.bbc.co.uk/sport1/hi/athletics/3078642.stm.

69 Heid Report, *supra* note 68.

70 WADA TD2004EPO, *supra* note 67.

71 See WADA document "Clarification About the EPO Detection Method" (29 September 2005), online: http://www.wada-ama.org/rtecontent/document/EPO_QA.pdf {"WADA Clarification"}.

72 WADA Clarification, *supra* note 72.

73 Duncan Mackay "EPO test flaws may be failing athletes" *The Guardian* (20 September 2005), online: Guardian Unlimited Sport http://sport.guardian.co.uk/athletics/story/0,10082,1573843,00.html.

74 There has been another controversy in the press involving the German sprint cyclist Hondo who held a Swiss racing license and was cycling for a Swiss team. He used a provision of Swiss law applicable only to litigation where everyone involved is of Swiss nationality or connection to have the cantonal court of Vaux (district of Lausanne, Switzerland) issue a stay suspending the first level finding of a doping infraction for the use of EPO until the appeals division of CAS has heard and determined the appeal. The circumstances were wrongly reported in some of the media as the CAS having reversed an EPO suspension. In fact it was the cantonal court provisionally suspending the application of the first instance arbitration decision to impose a two year period of ineligibility on Hondo. On 19 April 2006 Hondo finished second in the cycling season opener at the Tour of Lower Saxony in Germany.

75 *Supra*, note 74.

76 Monique Beullens *et al.*, "False Positive Detection of Recombinant Human Erythropoietin in Urine Following Strenous Exercise" (2006) Blood, pre-published online on 21 February 2006; DOI 10.1182/blood-2006-01-0028 {"Beke article"}.

77 Alamgir Khan, *et al.*, "New urinary EPO drug testing method using two-dimensional gel electrophoresis" (2005) 358 Clin Chim Acta 119-130 ["Kahn *et al.* article"].

78 *Supra*, note 72.

79 CAS 2005/A/831 {"*Hellebuyck*"}.

80 Beke article, *supra* note 77.

the testing result. At the hearing, Hellebuyck relied on one major point of criticism: the possible cross-reactivity of the EPO antibody. Hellebuyck introduced the scientific article written by Khan *et al.*[81] into evidence and argued that the potential cross-reactivity of the antibody introduced a serious risk of false positives. Hellebuyck also argued that the exoneration of Rutger Beke by the Flemish Disciplinary Commission demonstrated that the test for EPO was flawed. While the scientific article concerning Rutger Beke[82] was not available at the time of the hearing, the Panel decided to admit the article into evidence and to allow further submissions subsequent to the hearing.

In deciding this case, the Panel considered the testimony of expert witnesses for both parties to the dispute. The Panel did not only consider the new scientific evidence; it also weighed this evidence against previous scientific literature and jurisprudence concerning the validity and reliability of the test for rEPO. The Panel found that the claims concerning cross-reactivity of the EPO antibody were not sufficient to establish doubt about the reliability of the testing procedure. The Panel found that potential cross-reactivity of the antibody did not lead directly or indirectly to the conclusion that the testing procedure was unreliable. The Panel further stated that the case of Rutger Beke was not suitable for calling the reliability of the testing procedure into question. The decision of the Flemish Disciplinary Commission was not available, nor were the laboratory results and documentation from Beke's original positive test. Finally, the Panel considered the scientific article published by the scientists who had worked with Rutger Beke. The Panel pointed out that the scientific study was conducted on only a single subject. Further, the Panel found that, even if the study were correct, the depiction of the alleged false positive electropherogram shown in the article was clearly different from the electropherogram produced during Hellebuyck's testing procedure. Thus, the article was not sufficient to cast doubt on the results of the testing procedure carried out in Hellebuyck's case.

The difficulty presented by these challenges to the testing procedure is the time and cost involved to determine if CAS will accept the test as being reliable. It is frequently, especially for any one athlete, prohibitively expensive to challenge the test procedure. Given the current approach of CAS every individual case must challenge the procedure and be able to support that challenge with scientific expert testimony and reference to the scientific literature. This is not an efficient way to establish the legal reliability of a particular test. An alternative dispute resolution {ADR} mechanism needs to be developed to handle such legal objections to the testing procedure.

f) The Test for Darbepotien (Aranesp)

Both the *Meier* and *Hamburger* cases were released just prior to the Salt Lake City Winter Olympic Games in February of 2002. The famous trilogy of cross-country skiing cases arose dramatically on the last day of the Salt Lake City Games dealing with the artificial substance darbepoietin (or Aranesp), a wholly synthetic version of rEPO.[83] That synthetic version of rEPO was developed by the manufacturer to show up in the acidic band of the electropherogram. The result is very readily observed and creates no issues of interpretation similar to those of other rEPO forms. The result is a very clear and distinctive visual test that requires nothing more to declare the adverse analytical result.[84]

This refinement of the test was actually developed while the Salt Lake Games were ongoing. The CAS, in the cross-country skiing trilogy of cases, had little difficulty in describing why the test could be accepted. During those Winter Games, three cross-country skiers had the first positive tests for darbepoietin. Previously, EPO testing had been used to detect the presence of only rEPO. Darbepoietin (or Aranesp, the brand name) was slightly different from both endogenous EPO and typical recombinant EPO. Darbepoietin was a modification of the erythropoietin hormone that had been specially engineered to be more effective than rEPO in treating diseases such as anemia. One of the main benefits of using darbepoietin as opposed to rEPO is that darbepoietin has a much longer half-life in the body than rEPO. As a result, patients that required treatment for anemia required fewer doses in order to achieve similar results.

The first case involving darbepoietin involved two members of the Russian cross-country skiing team, Larissa Lazutina and Olga Danilova.[85] The IOC and FIS sanctioned both athletes, and both appealed those decisions to CAS, where their cases were heard together. Lazutina and Danilova claimed that the detection of darbepoietin was only experimental, and that it had not yet been legally or scientifically accepted. They further argued that it was not acceptable to use the test for detecting rEPO in order to detect a different substance, darbepoietin.

The CAS Panel deciding the merits of the case made a simple statement about what had to be shown in order for them to uphold Lazutina and Danilova's positive results and the scientific test that had led to those results. They stated that in addition to showing that the skiers' samples had been properly collected and the chain of custody was complete, the IOC had to prove that "the test used was a reliable test for the discovery of the presence of a prohibited substance."

The CAS Panel accepted the evidence of several witnesses who described the test used to detect both rEPO and darbepoietin and claimed that it was reliable, and preferred that evidence to the testimony of a witness who did not provide any direct evidence against the reliability of the test, but rather claimed that the test had not been sufficiently validated through publication and discussion in the medical community. Importantly, the Panel accepted testimony that there was no problem in detecting darbepoietin using the test that had been established for detecting rEPO, and that the test needed no modification. In conclusion, the Panel found that the methodology of testing for rEPO and darbepoietin was scientifically sound, and that the results produced by the tests were reliable.

There was also a positive test for darbepoietin at the Salt Lake City Olympics involving another cross-country skier, Johann Muehlegg[86] of Spain. Though Muehlegg's case was very similar to that of Lazutina and Danilova, Muehlegg's appeal to CAS was heard by a different Panel, who made findings about the EPO test procedure that supplemented those made by the Panel in the Lazutina and Danilova cases. The arguments that Muehlegg made in his defense were more extensive than those put forward in Lazutina and Danilova.

The Panel dismissed the first of Muehlegg's arguments regarding whether darbepoietin is a prohibited substance by finding that under the OMAC rules, "analogues and mimetics" of substances such as rEPO are also prohibited. The panel found that darbepoietin produces physiological effects that are similar to those produced by rEPO, and on an evaluation of all of the evidence found that darbepoietin was an analogue and mimetic of a Prohibited Substance.

The panel gave more consideration to Muehlegg's claim that the Salt Lake City lab that had performed the test had not been specifically accredited to perform that test at the time of the Games. The panel accepted Muehlegg's claims that the lack of accreditation to perform the specific EPO test in question did have the affect of rendering inoperative the presumption in favour of the laboratory. Importantly though, in Muehlegg's case, the Panel was quick to point out that the lack of accreditation was not fatal, and did not mean that the lab was not capable of conducting the EPO test. The Panel made clear what would be required in order to uphold the validity of the

81 Khan *et al.*, *supra* note 78.

82 Beke article, *supra* note 77.

83 *Lazutina* v/ *IOC*: CAS 2002/A/370 {"*Lazutina*"}; *Danilova* v/ *IOC*: CAS 2002/A/371; *Lazutina* v/ *FIS*: CAS 2002/A/397; and *Danilova* v/ *FIS*: CAS 2002/A/398; *Lazutina and Danilova v/ IOC*, 4P. 267/2002 (27 May 2003) (Swiss Federal Tribunal); *Muehlegg v/ IOC*: CAS 2002/A/374 {"*Muehlegg*"}.

84 The CAS Panel in *Muehlegg* made the following findings regarding the detection of Aranesp (or darbepoietin): *The Panel must conclude on all of the evidence before it that Aranesp has its own unique fingerprint which shows 4 bands clearly ... in the acidic range.* And in another section of the decision: *[T]he Panel concludes that the direct urine test employed to detect r-EPO can also be applied to detect Aranesp. The notable difference between the two applications is that Aranesp does not require a threshold safety margin to protect against false positives because of overlap, as does r-EPO.*

85 *Lazutina* v/ *IOC* CAS 2002/A/370; *Danilova* v/ *IOC* CAS 2002/A/371; *Lazutina* v/ *FIS* CAS 2002/A/397; and *Danilova* v/ *FIS* CAS 2002/A/398.

86 *Muehlegg*, *supra* note 84.

EPO test: "What must be established to the comfortable satisfaction of the Panel is that the testing procedure as carried out was in accordance with the prevailing standards and practices of the scientific community."[87]

After reviewing all of the evidence, the Panel did find that the testing carried out in Muehlegg's case was in accordance with the scientific community's practices and procedures. In support of its conclusion that the "direct urine test" used by the lab was a valid method to detect the presence of EPO, the Panel referred to numerous published scientific studies and several scientific meetings. Importantly, the Panel rejected Muehlegg's argument that the ongoing development of the direct urine test implied that the test was still in a trial stage and was therefore not valid. The Panel stated that "the fact that the laboratories wish to improve their testing methods, and further improve the rEPO test, does not result in the test being invalid."[88]

Muehlegg also criticized the lack of an objective threshold indicating the presence of darbepoietin. The Panel was nonetheless comfortably satisfied that there was unlikely to ever be any significant overlap between darbepoietin isoforms and endogenous EPO isoforms. The Panel found that darbepoietin had been engineered in such a way as to leave a distinctive fingerprint, which had been confirmed by scientific work. Therefore, the Panel found that EPO test that had been used to detect rEPO was also valid to detect the presence of darbepoietin, even without the use of objective thresholds, such as the 80% BAP threshold. The Panel found that the testing results established Muehlegg's use of darbepoietin without doubt.

The darbepoietin cases provide a discrete segment of EPO jurisprudence from other forms of rEPO. In accepting the test procedure the cases do not reflect any new developments in the CAS jurisprudence. However, they point up a deficiency in the overall system of hearing doping cases. Each case has to be heard individually and proven. The Salt Lake trilogy underscores in dramatic fashion the costs and time involved for the IOC who had to prosecute the cases. Each case required the scientific proof of the test in order for it to be acceptable and each athlete had to deploy their own experts to raise the challenges to the test. Once again the development of an ADR process for the acceptance of new scientific procedures or the evolutionary revision to prior procedures would cut costs and make the system more balanced and fair for all.

3. Blood Transfusion: A New Test Procedure

The emergence of the new test for darbepoietin EPO at the Salt Lake Winter Olympics and for blood doping by homologous blood transfusion at and subsequent to the Athens Summer Olympics have raised questions concerning the standard CAS will use to determine if an analytical testing procedure of the scientific community is acceptable to establish the presence of a prohibited substance. The pursuit of such cases is enormously expensive and very time consuming. They represent a different challenge to CAS but more particularly to the overall system of doping control and the determination of a doping offence.

The introduction of a new test for the detection of blood transfusions was the subject of a CAS appeal in the case of Tyler Hamilton.[89] As with the EPO and nandrolone cases the scientific analytical methodology leading to the conclusion of a doping infraction was challenged. Similarly, although the basic scientific methodology was a well-known and widely used analytical technique, known as flow cytometry, it had never been used before to sanction an athlete for the presence of transfused blood.

The flow cytometry technique is used to detect the presence of mixed populations of red blood cells. In almost all cases, a person's red blood cell population should be uniform as the characteristics of the cells are determined by genetics. Therefore, the presence of a mixed population of red blood cells should suffice as proof that there has been a transfusion of another person's blood. Flow cytometry distinguishes between different red blood cell populations based on differences in the presence of cell surface markers, similar to the major markers that determine blood types (eg. A, B, AB, or O). When conducting a transfusion, it is not necessary to match other minor cell markers, however. The testing procedure to detect transfusion exploits the differences in the presence of minor cell markers that would be expected if a transfusion had taken place.

Hamilton's challenge to the testing procedure used to detect homologous blood transfusions was based on two grounds. First, he argued that that testing procedure had not been sufficiently validated and that there had been a lack of proper control studies and examination of false positives. Second, he argued that even if his sample did prove the existence of a mixed red blood cell population, the mixed red blood cell population was not due to transfusion but rather due to chimerism, an extremely rare phenomenon where an individual's genotype can differ amongst different cells.

The Panel first addressed the issue of chimerism. Hamilton had taken a DNA test during the course of the hearing, the results of which indicated that he was not a chimera. This result was accepted as fact by the Panel despite the contrary opinion of one of Hamilton's expert witnesses.

Then, the Panel assessed the scientific merits of both the process of the flow cytometer test and the interpretation of the testing results. In this respect the challenge for CAS was no different than that it faced in *Bergman* in EPO testing or the various challenges in nandrolone testing. The Panel considered that the use of flow cytometry had an established history in the medical field, in contrast to the testing procedure used to detect EPO. The blood transfusion testing procedure was a test of identification, not measurement, and thus did not require a measurement of uncertainty or a percentage threshold. The blood transfusion testing procedure had been published in peer reviewed journals, and the experts of both parties agreed that the proof of principle of the test had been established.

The Lausanne laboratory that had performed the testing procedure on Hamilton's sample was not specifically accredited to perform the blood transfusion testing procedure. As noted in the cases of *Boulami* and *Muehlegg*, this lack of accreditation was not fatal, but simply placed the burden of proving that the test procedure was in accordance with the practices and procedures of the scientific community upon USADA and the UCI. The Panel discussed the development of the use of flow cytometry in sport, and came to the conclusion that at the time of Tyler Hamilton's positive test, the test as conducted by the Lausanne laboratory was valid and reliable. The Panel stated that the validity of the test had been accepted by the broader scientific community. Further, shortly after the time of Hamilton's positive test, the Lausanne lab received ISO accreditation to perform the blood transfusion testing procedure using a protocol that had only changed minimally and immaterially from the protocol used at the time of the Hamilton test.

The Panel also addressed the arguments raised by Hamilton suggesting that the test was unreliable. Notably, Hamilton relied on inconsistent statements made by some witnesses to impeach their credibility. However, the Panel found that the prior inconsistent statements were generally attributable to the exchange of contrary views during the development of the test, a time when it would be natural for those developing the test to look critically at how it was being implemented. As the tests were validated and accepted, these contrary views were reconciled. The Panel also addressed the many incidents of false positive results supposedly generated by the testing procedure that were alleged by Hamilton. The Panel examined each individual allegation, and determined that none of them were sufficient to suggest that the testing procedure as conducted on Hamilton's sample was likely to produce false positive results. Among the various reasons for the alleged false positives was that they were produced intentionally as an example, they were produced during a system malfunction which was noted in the result produced, or they were produced because of problems that had been fixed well before Hamilton's positive test.

In the end the CAS Panel was comfortably satisfied that the testing procedure as applied to Hamilton's sample was reliable. The test con-

87 *Ibid.* at para. 7.1.7.
88 *Ibid.* at para. 7.3.2.3.
89 *Hamilton*, supra note 6.

firmed the presence of a mixed red blood cell population which arose due to transfusion of another person's blood. Accordingly, it was held that Hamilton had committed the doping violation of homologous blood transfusion.

The *Hamilton* case decided by CAS was an appeal from a decision at the USADA level.[90] The validity and reliability of the test procedure was also challenged at that level, where the NACAS/AAA Panel dealt with the scientific evidence in the same way and came to a similar conclusion. The CAS appeal of that decision raises the same issue of the costs of scientific proof that arose in the darbepoietin cases after Salt Lake because the appeal is *de novo*. The sanction imposed upon the athlete at first instance was already into the second year by the time the result of the appeal was pronounced on 10 February 2006. The time and cost of this challenge was enormous. Once again, an ADR process to permit a single challenge on the testing procedure would be more efficient and effective for everyone and would remove the burden of these challenges on a particular athlete, international federation or national anti-doping organization.

4. Conclusion

The CAS has accommodated well to the changes in test procedures involving nandrolone and EPO substances. A review of the history of those substances in the CAS jurisprudence reveals how dependent athletes' cases are on the state of scientific knowledge at the time of the hearing. As science evolves, so to does the testing procedure. However, along with these evolutions comes the possibility that prior cases may well turn out to have been false positives, as will cases now being caught with the new test procedure.

The introduction of new test procedures as was done in part for Aranesp, and entirely for blood transfusions, suggests that while CAS can adapt and accommodate the challenges to the procedure and make reasoned conclusions, the costs of the challenges in the initial cases is enormous for both athlete and international federation. A better system of developing acceptance for new test procedures must be found. I would suggest that an alternative dispute resolution process would be a less costly and more effective system for resolving testing procedure issues than the one off challenges now undertaken in these matters.

90 *USADA v/ Hamilton*, AAA No. 30 190 00130 05 (2004).