In the days leading up to the 2008 Olympic Games in Beijing, a number of scientific journals published special issues (1, 2) or critical commentaries and opinion pieces regarding the antidoping movement. For example, an analysis of antidoping policy by Kayser and Smith (3) presented criticisms based on ethical arguments (4). On the other hand, equally persuasive ethical arguments supporting antidoping policies were reported by Murray (5). In addition, the public statements released by the defense team before each of the 2 arbitration hearings for Tour De France winner Floyd Landis, at which he was convicted of committing a doping violation, vehemently attacked the laboratory and the staff that performed the test. These public attacks were by advocates for the defendant, and the antidoping rules prevented a response to these charges. My purpose here is to provide an overview of how the current antidoping rules came into effect, to review some of the science underlying the antidoping rules, and to discuss a few of the cases decided by the Court of Arbitration in Sport (CAS).2

The fight against performance-enhancing substances began in the 1920s, long before there were testing methods for the prohibited substances. For years, the leaders of sport went it alone in this fight. Some critics argued, and continue to argue, that sport leaders have an issue similar to the “fox guarding the henhouse” when it comes to overseeing drug-testing programs. A major shift occurred in 1999, when the World Anti-Doping Agency (WADA) was formed as an independent body to harmonize antidoping practices, and independent national antidoping organizations such as the Australian Sport Drug Agency, the Canadian Center for Ethics in Sport, and the United States Anti-Doping Agency (USADA) began to emerge. WADA was established as a Swiss foundation with the support of intergovernmental bodies, governments, public authorities, and sports organizations. A Foundation Board made up of equal numbers of representatives from government and sports bodies governs the agency. WADA receives half of its funding from government dues and half from international sports organizations. An international consensus process that began in 2001 developed the World Anti-Doping Program. The core of this program was the World Anti-Doping Code (Code) (6) that set out the definition of doping and the rights and responsibilities of athletes, antidoping agencies, sport governing bodies, and governments. The Code was adopted at the Copenhagen Second Conference on Doping in Sport in March 2003 and went into effect on January 1, 2004. Because governments cannot sign treaties with nongovernmental bodies like WADA, a United Nations Education, Science, and Cultural Organization International Convention against Doping in Sport was passed in October 2005 (7). To date, 107 governments, including the US government, have signed the convention, thus basically indicating their agreement to support the WADA Code in their laws. In addition to the Code, the World Anti-Doping Program includes 5 mandatory documents: the Prohibited List International Standard (8), the International Standard for Laboratories (9), the International Standard for Testing (10), the International Standard for Therapeutic Use Exemptions (11), and the International Standard for the Protection of Privacy and Personal Information (12). The Code recently underwent a second 18-month review and consultation process, and a new revision of the Code was approved at the Madrid Third Conference on Doping in Sport in November 2007. Substantial changes were incorporated into version 3 of the Code, which went into effect on January 1, 2009.

The Code defines doping as the presence of a prohibited substance, in any amount, in the athlete’s urine or blood sample. The only exceptions are for substances that are produced naturally in the body that have threshold concentrations (see below). Intent is not required for a doping violation. The Code defines the rights of the athlete in an antidoping rules violation.
It requires that the CAS arbitrate antidoping rule violations. In the US, the Ted Stephens Olympic and Amateur Sports Act mandates that the American Arbitration Association hear all eligibility disputes related to Olympic and Paralympic sport. The USADA and US Olympic Committee rules require that the American Arbitration Association arbitrators chosen to hear antidoping cases also be members of the CAS. The American Arbitration Association panel is independent of USADA. The athlete and USADA each have the opportunity to select 1 arbitrator, and those 2 arbitrators choose the chair of the arbitration panel. In general, arbitration is thought to be faster and less expensive than litigation. For an international enterprise like elite sport, advantages are also derived from the fact that arbitration awards are generally recognized across national borders, and the program does not have to deal with individual national laws. Arbitration also can establish rules that take advantage of expertise of the arbitrators in a narrow field such as international sport disputes and doping. In fact, arbitration does not require that lawyers be the decision makers, although CAS requires legal training as a prerequisite of membership.

The antidoping rules contained in the World Antidoping Program are required to be incorporated in the rules of the sports organizations that participate in the Olympic and Paralympic Games. They are no different from the rules that determine the size of the playing field or the equipment used in the game. The athletes agree to the antidoping rules as a condition of competing in the sport. When the athlete violates the antidoping rules, it is very much like misconduct in the legal or medical professions. The Code also establishes the burden of proof in the arbitration of an antidoping rule violation, which is “to the comfortable satisfaction of the panel given the seriousness of the allegation.” This burden of proof is very similar to that adopted, for example, by the American Academy of Forensic Science, for ethical violations. Professional misconduct in the medical, pharmacy, nursing, or legal professions, which could result in the loss of a professional license or enrollment in a stringent drug-monitoring program, have similar burdens of proof. Although it has been suggested that the burden of proof should be “beyond reasonable doubt”, the lack of ability of the antidoping programs to compel testimony and their very limited investigative or subpoena powers to obtain additional evidence make this model a poor fit for antidoping proceedings.

One of the primary reasons for having a list of prohibited substances and methods is to protect athlete health. The reported side effects of anabolic steroids associated with the German Democratic Republic doping program (13), particularly in young women, illustrate the need for oversight. Although some may consider this purpose to be paternalistic or irrelevant relative to other risks taken during training and competition, it is important to consider the coercive impact of successful drug users on other competitors. To be placed on the List, a substance must fulfill 2 of the following 3 criteria: (a) poses a potential risk to the athlete’s health, (b) has the potential to enhance performance, and (c) violates the spirit of sport.

The List Committee consists of a group of 11 internationally known scientists who annually review the substances on the List and any new classes of potentially performance-enhancing classes of substances or methods using these criteria. The List is distributed to stakeholders for comment by June of each year. After consideration of stakeholder input, the List Committee, the WADA Medical, Science and Research Committee, and the WADA Foundation Board approve a final version of the List by October for implementation in January of the following calendar year.

The procedure for collection and testing of specimens for doping control involves a large number of protections for the athlete. After a sample is collected under full observation, athletes are afforded the opportunity to select a transportation kit, to transfer their urine to the A and B bottles in the kits, to ensure that the ratchet security mechanism on the bottles is locked, and to see the bottles returned to the transportation container. The laboratory is blinded to the identity of the athlete during the analysis of the urine in the A bottle. If an adverse analytical finding is reported for the sample, the athlete may send a representative to the laboratory to verify the identity of and security of the B bottle and to observe the analysis of the urine. In the Landis case, 2 lawyers and a technical expert represented the athlete’s interests while an additional 2 scientific experts represented antidoping organizations.

Although those working in workplace drug testing appreciate the cottage industry that has developed around “beating the test,” the athletic community has taken this industry to a higher level. Access to unethical health professionals and other advisors has greatly increased the sophistication of both doping and masking strategies. For example, scientists have advised athletes to have pharmacokinetic studies performed, stating:

“... However with enough resources the exact dosage to be clear in 10 h or less could be determined quite easily. From this perspective it would seem that the only rider ever caught using EPO would be the one unlucky enough not to have had the money to gain access to top doctors and researchers working in laboratories to gain the knowledge of exact excretion rates (Anonymous e-mail obtained by USADA, 2005).”
Athletes have placed “rice grains” containing proteases into their penile urethra (14) and placed protease powder under their fingernails and urinated over their fingers in an attempt to destroy the recombinant erythropoietin in their urine sample during transport to the laboratory.

The Code requires that antidoping tests be performed in laboratories recognized by WADA. (In the Code, WADA recognition is referred to as “WADA accreditation” although WADA is not a formal accrediting body.) To obtain WADA recognition, the laboratory must have the support of a national antidoping organization, obtain and maintain International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025 accreditation, and successfully participating in the WADA external quality assessment scheme (EQAS). Testing laboratories of many types may be assessed against ISO/IEC 17025, General Requirements for the Competence of Testing and Calibration Laboratories. The International Standard for Laboratories was drafted as an expansion to ISO/IEC 17025, as contemplated in Annex B of the standard, for specific fields of analysis. A national accrediting body that is a signatory to the International Laboratory Accreditation Cooperation arrangement assesses the antidoping laboratory against both ISO/IEC 17025 and the International Standard for Laboratories. As a general statement, accreditation indicates the competence of the laboratory to perform tests that are within its scope of accreditation. The use of an international system such as ISO/IEC 17025 reflects the international nature of Olympic and Paralympic sport. The WADA EQAS includes both blind and double-blind samples, most of which are urine specimens obtained after administration of a prohibited substance (15). The EQAS also includes educational proficiency tests that are designed to assist in the harmonization of laboratory performance.

The first antidoping tests were developed in the 1960s (16). The Cologne Workshop on Dope Analysis (Workshop) began in 1983 as a way to share the latest information among the staff of the accredited laboratories. The proceedings of the Workshop have been published since 1991, and are available through Sportverlag StraB or can be downloaded from the Deutsche Sporthochschule Köln Institut für Biochemie Web site (http://www.dshs-koeln.de/biochemie/). A substantial fraction of the reports published in the proceedings have been published in the traditional peer-reviewed literature. A recent review (17) of the analytical chemistry of detecting performance-enhancing drugs documented publication of more than 150 papers on antidoping science in the peer-reviewed literature over the last decade. Many of the other contributions would be considered by many journals to be of insufficient interest to their readership to publish owing to the nature of routine antidoping testing. As one example, I authored a paper on the inhibition of caffeine metabolism caused by fluvoxamine (18). The information was relevant to a doping case involving an athlete (who, as a result of our laboratory work, was not sanctioned) and made other antidoping laboratories aware of the potential issue, because at that time a urinary caffeine concentration >12 mg/L was prohibited.

Berry (19) and the editors of Nature (20) were critical of the science supporting the antidoping rules. Although Berry’s statistical reasoning was sound, his apparently limited knowledge of the underlying science of steroid testing and metabolism led him to erroneous conclusions. Conditional probability is well recognized by the antidoping community [e.g., (21)]. For synthetic anabolic steroids, Berry’s statements regarding the potential for naturally occurring metabolites is simply not true. Berry seems also to fail to appreciate that the use of confirmation tests and the detection of multiple metabolites greatly increases the likelihood ratio that the test results are associated with use of prohibited substances. Berry also questioned the process involved in establishing thresholds for naturally occurring prohibited substances. To establish a threshold for human chorionic gonadotropin concentrations in the urine of male athletes, Laidler and coworkers (22) analyzed 1400 urine samples and established a “far outside” limit of 5 IU/L. An additional 120 samples from noncompeting athletes were tested and shown to fall below 5 IU/L. To ensure that no false-positive results were reported, the recommended and initially implemented human chorionic gonadotropin threshold was 10 IU/L. Subsequent work justified the lowering of the threshold to the current value of 5 IU/L. The population distribution of the testosterone-to-epitestosterone ratio in urine for both male (23–26) and female (24, 26) athletes has been published. The number of tests in the populations now numbers in the tens of thousands from each of several laboratories, and the results are statistically indistinguishable. In addition to the implementation of individual-based reference ranges (21, 25) rather than the population-based ranges mentioned above, tests have been developed that can detect the difference between natural and synthetic testosterone (27). More recently, Walker and colleagues (28) published a study of 1200 women that showed that none of them exceeded the WADA threshold for norandrosterone.

In addition to publications in peer-reviewed journals, many of the scientific studies carried out by antidoping organizations are presented and discussed at scientific symposia. Since 2002, USADA has organized an Annual Symposium on Anti-Doping Science to which about 90 scientists and others from the antidop-
ing community and area experts from the international academic community have been invited. In 2004, the symposium topic was human growth hormone, and the recommendations made by the conference attendees led directly to further studies before the growth hormone (GH) test was implemented. Discussions at the Annual Symposium have led to the direction of USADA research funds to a broad range of activities, from the development of reference materials to a study on the effects of injury on the biomarker assay for GH abuse (29). Some scientists and statisticians who attended the meeting also agreed to serve on a working group that has continued to advise USADA and WADA on GH research results. The recommendations of this group were considered before the GH isoforms test was implemented in July 2008. A description of the GH isoforms method was recently published (30). Topics of other USADA Annual Symposia have been enhancement of oxygen transport, gas chromatography/combustion/isotope ratio mass spectrometry, muscle growth and recovery, subject-based reference ranges, and mitochondrial manipulation to enhance energy production.

One seemingly universal position taken by athletes who have an adverse analytical finding is to deny, deny, deny. Before 2009, the Code and rules forbade antidoping organizations from responding to any comments from the defense team. This prohibition made one-handed coverage of the issues in the press impossible. The Code is written in such a way that an athlete trying to avoid a sanction can attack only the collection process and the laboratory results. For those who have not been involved in the legal system, it is important to understand that the athlete’s lawyer advocates on behalf of the athlete. There may be no better example of the advocate role of defense counsel than in the Landis case, in which the defense threatened to “take down the Paris laboratory in an embarrassing way” (31). The different roles of the scientist-expert and the lawyer-advocate can put the expert in a difficult position. The duty of the expert is to assist the finder(s) of fact in understanding technical issues in their area of expertise, regardless of the party paying them. In my opinion, performance of this role requires experts to impartially review all of the evidence for which they have expertise and to draft a report that considers all of the information, just as they would in reviewing a manuscript submitted for publication. The Landis Court of Arbitration for Sport opinion (32) stated “The Panel also finds much force in Respondent’s contention that ‘Appellant’s experts crossed the line, acting for the most part like advocates for Appellant’s cause and not as scientists objectively assisting the Panel in the search for the truth.”

In numerous cases, scientists have believed the athlete’s protestations of innocence, possibly lost their perspective, and sought any alternative explanation for the adverse analytical finding, only to hear the athlete confess to doping at a later time. Examples include the cases involving Dennis Mitchell, Adam Bergman, Genevieve Jeanson, and Marion Jones. This observation in no way suggests that athletes are not innocent until proven guilty or that the athlete should be denied competent scientific expertise. But when the scientist places into testimony his or her own partisan position about guilt or innocence or the burden of proof required, s/he has become an advocate. Both the judicial system and the scientific community are concerned about the increasing partisanship of experts. In highly technical cases, such as doping, the entry of scientific evidence through examination and cross-examination can be difficult. Scientists should assist the legal field in improving the entry of technical information. One approach that has been adopted in the Australian judicial system is the concept of “concurrent evidence” (33). In this approach, the experts testify simultaneously and may ask each other questions. The idea is to provide the finders of fact with a better understanding of the highly technical issues.

Another example of advocacy is The Wiki Defense: How the French Lab (LNDD), US Anti-Doping Agency, and AAA Arbitrators Failed: Floyd Landis Doping Test 995474: The Science Summarized. 2nd ed. Revision 73, posted by Arnie Baker (34). Landis sought free scientific advice by posting 370 pages from the Laboratoire National de Dépistage du Dopage (LNDD) laboratory documentation package (there were more than 4000 pages of laboratory evidence) on a Web site and using message boards and online communities to identify “errors” to exploit in his defense strategy. Landis called this his “Wikipedia defense.” One flaw in this “wisdom of the masses” strategy is that instead of actually studying the entire content of the documentation package, the “errors” tended to be viewed in isolation from the rest of the data. As an example, Baker claims that the laboratory should have aborted the analysis because of bacterial contamination. He bases this on the report of the GC-MS results for the free fraction of epitestosterone, in which there is a small “concentration” in the sample. There are 5 facts in the documentation that constitutes more than 5% of the epitestosterone glucuronide concentration in the B sample. There are 5 facts in the documentation that show Baker is wrong: (a) examination of the peak that Baker relies on shows that it is not at the correct retention time for epitestosterone despite the fact that the computer-generated data report labeled the peak as such; (b) the same measurement in the A sample does not exceed the 5% criteria; (c) the concentration of testosterone in the free fraction is much less than 5% of
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the testosterone glucuronide concentration, and having only 1 steroid degraded is inconsistent with what is known about bacterial degradation of steroids; (d) 5β-androstane-1,3,17β-trien-3β-ol, another marker of bacterial growth, was monitored in the laboratory’s method and was not present in Landis’ sample; and (e) Landis’ urine sample was transported frozen and arrived at the laboratory within 8 h of collection—conditions inconsistent with bacterial growth. All of this information was present in the documentation provided by the Paris laboratory. Finally, the gas chromatography–combustion–isotope ratio mass spectrometry (GC-C-IRMS) method that was the basis of the doping charge is not affected by bacterial contamination.

Some criticism has been directed at the discovery process in antidoping arbitration. For example, to avoid unrelated testimony that wastes time and resources, the process requires that the athlete must show any laboratory miscues caused the adverse analytical finding. An example from the Landis case was the insistence by Landis’ experts that failure to remove the lifting rings from the magnet of a GC-C-IRMS instrument (not used in the analysis of Landis’ sample) could cause distortion in the magnetic field. This testimony was intended to demonstrate lack of competence by the LNDD laboratory staff, despite the facts that the instrument was installed by the manufacturer and met specifications with the lifting rings in place, that controls were accurately measured, and that LNDD’s scope of ISO/IEC 17025 accreditation included GC-C-IRMS.

In conclusion, it should be appreciated that international elite sport is indeed a global enterprise, and the development of the World Anti-Doping Program was the result of an international consensus process that included athletes. Much of the scientific basis of antidoping tests has been published in the peer-reviewed literature, frequently in Clinical Chemistry. It should also be appreciated that lawyers, as advocates for athletes (or antidoping organizations), are not necessarily the best source of impartial information, especially when only one side is heard.

In an era in which the highest paid athletes in numerous sports receive salaries of tens of millions of dollars per year, the support provided for antidoping research, education, and testing is embarrassingly inadequate. Despite the limitations imposed on the system, the antidoping system has made significant gains in the last 8 years. The requirement for athlete whereabouts during training periods and the off season has increased the success rate for out-of-competition collections. The successful prosecution of “nonanalytical” doping cases based on documents obtained from law enforcement arising from the BALCO (Bay Area Laboratory Co-Operative) case involving the performance-enhancing steroid tetrahydrogestri none, insulin, growth hormone, testosterone, and epitestosterone transdermal creams, and the lifetime bans given to 2 coaches involved in doping are further illustrations of progress. The development of detection methods for several erythropoiesis-stimulating drugs (e.g., Darbepoetin, Mircera) before their introduction, and the detection of athletes using them show the increased cooperation between the pharmaceutical industry and the antidoping movement. The challenge for the next eight years is to continue to build on the scientific advances and to harmonize the testing of athletes globally. The international antidoping system works, and it will only get better if it is given a chance.

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References


