Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

The fight against performance enhancing substances in sports began in the 1920s, long before there were testing methods for the prohibited substances.

For years, the leaders of sport battled alone until a shift occurred in 1999, that's when the World Anti-Doping Agency, or WADA, was formed as an independent body to coordinate anti-doping practices among organizations.

Dr. Larry Bowers' article in the August issue of *Clinical Chemistry* addresses the anti-doping system. Dr. Bowers is the Chief Science Officer for the US Anti-Doping Agency and served as an Independent Observer for WADA at the Sydney Olympic Games and he's our guest in this podcast.

Tell us, Dr. Bowers, what have been the benefits of a worldwide anti-doping movement?

Dr. Larry Bowers: Well, the primary benefit has been a more harmonized system; sport no longer has to combat doping alone. We have governments now as a partner in the fight against the cheaters.

In my opinion great progress has been made and I anticipate it will continue. Being able to celebrate a truly amazing effort by the athlete based on 100% their work and effort I think is a really special thing, and I'd like to see us get back to that and that's really part of the benefit of a worldwide system.

Host: So from your experience what are the responsibilities of science experts in providing testimony or other consultation during anti-doping cases?

Dr. Larry Bowers: Individuals engaged as expert witnesses are expected to assist, in our case, an arbitration panel, but in court it would be the court and the jury to understand difficult technical issues.

Despite the fact that the expert may be paid for their time by one side or the other, their job is really to help scientifically naïve finders of fact whether it be a jury or a panel of judges understand the science.

Lawyers on the other hand are really there to advocate their client's position, and they don't necessarily make it clear to scientists or experts what their responsibilities are, I think, in part for self benefit.

In my opinion if the expert is really to assist the finders of fact and understanding, they really have to carefully review all of the data; it's sort of like reviewing a grant or reviewing a paper for publication.

So occasionally I encounter some individuals who either function as part of the advocate team, which is really not what their responsibility is or in other cases who have not thoroughly reviewed or understood the data that they presented with in the case.

Host: With that in mind what does it mean for a laboratory to be World Anti-Doping Agency accredited?

Dr. Larry Bowers: Well, international sport testing is really a global enterprise. The laboratories play a really critical role in the fight against cheating by the use of performance enhancing drugs.

WADA's recognition of the importance of the labs has really led them to a fairly intensive laboratory evaluation process. The first thing is the lab has to be assessed against ISO 17025, which is an international standard for the competence of laboratories. That assessment affirms the competence of the laboratory to perform the tests that are within their scope, and the scope is really laid out in the WADA Standards and WADA Technical Documents, so you can see how they sort of fit together.

Through interactions between WADA and a group called the International Laboratory Accreditation Cooperation, or ILAC, there is an assessment also against the WADA Standards and Technical Documents by an independent national accrediting body.

So the accrediting body looks not only at ISO 17025, but also the labs compliance with the WADA Standards and Technical Documents.

WADA also operates an external quality assessment system, which also would be evaluated during that independent assessment that I just talked about and interestingly, the WADA system incorporates both blind and double-blind samples. So the laboratory actually received samples that it has no idea that it's a quality assessment sample. So there's a very rigorous program that goes on for recognizing laboratories by WADA.

Host: Can you compare anti-doping efforts in the Olympics before and after the formation of the World Anti-doping Agency and how did those programs under WADA differ from those in US professional sports?

Dr. Larry Bowers: Prior to the formation of WADA and also national anti-doping organizations, like the US Anti-Doping Agency in about 2000, the International Olympic Committee was arguably the overseer of anti-doping standards.

I say arguably because, in fact, each sport federation voluntarily complied with the IOC rules and really operated under its own rules at all times other than at the Olympic games when the IOC truly had oversight of the anti-doping enforcement.

The fact that there were all these different systems some similarities and some differences led to uneven rules and unequal enforcement. In addition many of the critics felt that the situation was analogues to the fox guarding the henhouse.

So a little of bit skepticism about whether or not sports would actually catch and sanction the athletes that they on the other hand advertise to the public and get them to come to their sporting events to follow. With the formation of WADA there was really an independent transparent set of eyes in the anti-doping.

It also reinforced the fact WADA did that in addition to just testing education and research were important components of an anti-doping program.

The WADA agreement brought governments into the anti-doping movement as more significant stakeholders and the WADA Code clarified the rights and responsibilities of athletes, anti-doping organizations, and governments. And maybe the most important thing that's happened since WADA's formation has been that WADA has an oversight responsibility to ensure the Olympic and paralympic sports federations and athletes complied with the code. So there's a real oversight, now, that was not there perhaps with the IOC and pre-WADA situation.

With regard to professional sports it's kind of interesting; the anti-doping rules are just like other rules of sport like the height of the rim in a basketball game or the distance from first to second base in a baseball game, and those rules are made by the people responsible for the game.

In professional sport some of those rules are negotiated between the owners or the management counsel and the players union and as a result the product of a negotiation not necessarily the product of a programmatic decision.

A good example of this is that in Olympic sport there is what's called an "open list" of prohibited substances and what that means is that in addition to listing a number of

compounds that are prohibited at the end of the category there's sort of catchall phrase such as "and related substances."

The purpose of that phrase is to make the program flexible enough so that they can deal with things like designer steroid used in a clandestine doping program and that the athlete can be potentially sanctioned.

A good example, again, of that would be USADA after the BALCO scandal spent a good deal of time, effort, and money trying to prove and eventually successfully before the court that tetrahydrogestrinone, or THG, was, in fact, an anabolic steroid. It had previous to that particular case never been characterized or in the public eye and so it was something that needed to be done.

In contrast to that, most of the professional league lists are closed and that means that if the compound is not specifically listed then it's not really prohibited.

One last point is, again, unlike Olympic Sport, most of the professional sports operate their only anti-doping programs and again that causes some critics to liken the situation to the fox guarding the henhouse.

Host: So what are some of the significant milestones made since the first anti-doping tests were introduced back in the 1960s and do you think that authorities have gained the upper hand?

Dr. Larry Bowers: Well, great question. Like science in general, a lot of the advances in anti-doping testing are linked to advances in the analytical technology.

So some of the milestones that have happened since the 60s would include the 1983 Pan Am Games where gas chromatography-mass spectrometry testing for steroids was used for the first time and that resulted in a number of positives and many withdrawals from the competition because athletes knew it was against the rules, but had never been tested rigorously for that class of compounds.

Another milestone would be the '88 Seoul Olympics and the fact that Ben Johnson was actually stripped of his gold medal for a violating of the anti-doping rules.

Another interesting milestone was the introduction of recombinant proteins and in particular recombinant erythropoietin and subsequent methods to detect the use of EPO and, again, you might think of one very significant example, which was the detection of a couple of medal winners at the Salt Lake City Olympics for the use of

Aranesp, which to that point had not been detected in doping before.

Some other milestones I think are not related to testing. I think the formation of WADA and the formation of national anti-doping organizations like USADA were really watershed moments for the anti-doping movement.

For the first time, there was a full-time agency trying to figure out what athletes were doing and trying to act as a deterrent. I think it was really important with the formation of those two groups that the concept that it will take more than testing to battle doping or cheating, was a key step forward, and we are now moving on to things like the use of intelligence that are collected from tips or information collected by law enforcement to assist in test planning and test execution.

Lastly, I think the incorporation into the WADA Code of the ability to sanction coaches and other athletes support personnel who facilitate doping is another really important step forward, so lots of important milestones, many of them since 2000.

Host: And do you think we are getting the upper hand?

Dr. Larry Bowers: I think there's been some indication of that. A good example would be the detection of Sera, which is a PEGylated version of Erythropoietin in the Tour de France last year in 2008. That drug was not previously on the market, it was detected because of cooperation between the anti-doping agencies and the pharmaceutical manufacturers and so things like that I think are letting us get the upper hand in specific areas, yes.

Host: In your opinion, is it going to be an end to the cat-and-mouse game between dopers and the authorities working to catch them?

Dr. Larry Bowers: Well, if the mouse stops, yes; but I think you raise an interesting point and an important point and that is that anti-doping is really based on a model called "perceived deterrents."

I really dislike using the analogy to the police, but I think I need to, sort of, do that to make the point. Think about what happens to traffic speeds when you see a police car by the side of the road, potentially somebody that has a radar gun. The traffic obeys the speed limits, which are a set of rules that have been agreed to for the good of the whole.

On the other hand, the ability to catch and sanction those who cheat is also important and, again, going back to the

traffic example would those same drivers be deterred from speeding if the police car was always at the same place everyday and the driver saw that no one ever pulled over even the most egregious speeders and I think the answer to that is no.

So, it's important that we able to catch people; it really doesn't give any of us a great deal of pleasure to that, but it really is an important part of the deterrents program. This also gives me a good chance to talk a little bit about education. Education, as I mentioned before, is really important.

USADA has two programs one is called 100% ME, which was really aimed at 5th and 6th graders beginning to make decisions on their own about things including drugs, and also another site called That's Dope, which is really directed at more of the teenage years and both of those are available on USADA's website, it's usada.org.

But the important part is that we are working to get those programs into schools and, hopefully, the next generation of athletes will be better informed and make better choices than some of the athletes in the past.

Host: Well, finally what are we doing to stay ahead of those who follow the science and work to circumvent anti-doping effects?

Dr. Larry Bowers: Well, I think a really important piece of this is that having a consistent anti-doping program with full-time scientists allows us to do a lot of things that we couldn't do before.

Back in the days before WADA and USADA there were committees that used to meet essentially four times a year over the weekend and spend those eight days trying to decide what would be good things to do in anti-doping, meanwhile the dopers who are out there spending 365 days trying to figure out how to beat the system, and so it was never an even fight before now.

The second thing that having some consistency in the administrative side of the anti-doping movement. One of the things that it does is it allows us to work with pharmaceutical companies, and I gave you the example of Sera before to obtain reference materials and to develop tests in conjunction with those companies before athletes get access to the drugs.

So, catching cyclists with things like Sera or the cross country skiers with an EPO derivative really comes about because of our ability to work ahead rather than catch up from behind.

Another thing that I think is really important is that sanctioning coaches and others who facilitate doping is also a step forward. USADA has formed an alliance with American College of Sports Medicine and a number of other professional organizations called Professionals Against Doping in Sport, or PADS, and one of that reasons that we started that program was to educate physicians about the use of steroids and other performance-enhancing substances in the hopes that they would talk to their patients about those issues and do it from an educated perspective, but also a part of the program is to contemplate sanctioning those healthcare professionals who may violate their Hippocratic Oath and assist athletes in doping.

Finally, to get ahead of the dopers there are a number of organizations that have sprung up. One example is the Partnership for Clean Competition, or PCC, that support anti-doping research.

In addition to developing new tests, for example, the research supported by the funds from these organizations has really answered some interesting clinical questions.

For example, it was known for decades that a small subset of individuals have a low urine ratio of testosterone to epitestosterone, but it really it wasn't understood why. Research has now shown that this is due to a double deletion of the UDP-glucuronosyltransferase 2B17 gene, and, so that's a very interesting piece of information.

Knowing that and blending that in with other kinds of clinical research that's done not only has helped anti-doping, but I think it's also benefited the clinical community, and I encourage the clinical chemistry community and the toxicology community to visit the PCC website, which is cleancompetition.org and see whether or not any of their research ideas might be of benefit to going forward in the fight against doping.

Host: Dr. Larry Bowers is the Chief Science Officer for the US Anti-Doping Agency and has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

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