Doping in Sport: From Strychnine to Genetic Enhancement, It's a Moving Target

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Thank you for that kind introduction.

I want to begin today by taking a moment to recount an event that took place more than 100 years ago.

The year was 1886, a period characterized by the genesis of new industries and the creation of great wealth. A period when we believed anything was possible. A period, in short, much like today.

1886 is a significant year for our conference because it marked the first recorded fatality from a performance enhancing drug.

An English cyclist died of an overdose of what is only known as "trimethyl", during a race between Bordeaux and Paris.

Of course, in the more than 100 intervening years, doping in sports, like the rest of technology, has grown in scientific and ethical complexity.

Indeed, so complex is this issue that we will see later in my remarks how we cannot even agree on precisely what constitutes doping – and these dueling definitions point to the heart of the problem.

The multi-stranded nature of the subject of doping is also reflected in the diversity of backgrounds of the participants here today.

In fact, looking over the list of this conference's attendees, I noted that only four participants in this conference are physicians. That's not as surprising as it might seem on the surface. It reflects the longstanding traditional orientation of the medical establishment.

Back when I was in medical school, our focus was on how drugs benefitted patients. After all, by statute, physicians are the ones who write prescriptions. Physicians are the conduit for new drug development with the scientific community.

Our principle concern, as physicians, was, and is the proper use of drugs, not their abuse.

Doping in sports was a subject that only a handful of physicians cared about. I suspect we barely spent 30 seconds on the subject in pharmacology. However, the same as with other forms of drug abuse, that is, sadly, no longer sufficient.

As my opening story suggests, the use, misuse and abuse of drugs have long shaken the foundations of both amateur and professional sports.

Competition, at its most basic level, appears to drive athletes to do whatever it takes to win. Perhaps the need to win at all costs is a Darwinian response, an adaptive mechanism, but we will leave that thought for another day.

We've seen that the problem is not new. History demonstrates that since recorded history began, athletes sought a competitive advantage by using various substances we call ergogenic aids.

Even as long ago as the 3rd century B.C., the Greeks, inventors of democracy and the Socratic method, were known to ingest hallucinogenic mushrooms to improve athletic performance. In the Roman era, gladiators used stimulants in the famed Circus Maximus (circa 600 B.C.) to overcome fatigue and injury, while other athletes experimented with caffeine, alcohol, nitroglycerine, opium and even the potent stimulant, strychnine.

Fast forward.

A new inflection point of abuse appeared in the 1950s with anabolic, androgenic steroids.

How prophetic were the words of Olga Fikatova Connolly, when in 1956, she proclaimed: "these awful drugs (anabolic steroids) have changed the complexion of track and field."

So did amphetamines change sports.

In the 1960s, the Danish cyclist, Knud Jensen and the English cyclist, Tommy Simpson died when their search for one kind of speed brought them fatally to another.

Remarkably, though the testing of horses for performance enhancing drugs dates back to 1910, the testing of humans for drug use in sports is a phenomenon of only the past quarter century.

It was as recent as 1965 that Arnold Beckett first applied sensitive gas chromatographic techniques to monitor drug abuse at an athletic event, the Tour of Britain cycle races.

And it was only in 1968 that the IOC medical commission actually published a banned list of drugs for the 1968 winter Olympics.

The introduction of the banned list was coincident with the development of new technologies in the laboratory and this confluence set the stage for a 35-year contest between those determined to

gain an unfair athletic advantage by using drugs and the forensic detectives of the laboratory.

It's a struggle between the manipulators versus the investigators and each side's armaments grow more advanced each day.

Since the 1960s, an explosion of science and technology have brought countless new drugs to market, black and otherwise.

In what seems to be a variation of newton's third law, which states that "For every action there is an equal and opposite reaction," it appears as if for every new drug that is developed, some athlete, determined to gain athletic advantage, will misuse or abuse that drug. This should come as no surprise. We live in a culture where individuals seek to maximize performance by what ever means available.

Let's examine steroids as an example of newton's third law meeting sports.

First isolated, structurally identified, and synthesized in the 1930s, anabolic steroids were used to promote a positive nitrogen balance in starvation victims and as a means of hormone replacement for those deficient in testosterone by means of disease or trauma.

New, positive applications of steroids continue to emerge. As recently as April 1999, two articles were published in J.A.M.A. exploring the therapeutic uses of anabolic steroids in the management of aids, and in dialysis patients.

Unfortunately, since its initial isolation in the 1930s, it didn't take long for anabolic steroids to become widely misused and abused by athletes - a problem that continues to plague sports to this very day.

And as science marches on, abuse is not far behind.

Some twenty years have passed since the first recombinant DNA molecules were constructed at Stanford University. Since then, the applications of genetic engineering, that is the artificial manipulation of the genetic code, have been numerous.

The techniques of altering the DNA of cells in order to change or produce biologicals has given rise to human growth hormone and to erythropoietin, to name but a few.

Recombinant human growth hormone means normal height for children otherwise destined to be dwarfs, but for the drug abusing athlete it means bigger, albeit not stronger, muscles. Erythropoietin means renewed vitality for those with anemia, but for the drug abusing athlete , it means greater endurance.

The dramatic abuse of the latest biotechnology breakthroughs crystalizes the need for an accepted

working definition of the word doping.

This definition sits at the heart of any doping control program. Doping, a term that derives from the Dutch word "doop" referring to a viscous opium juice that was the drug of choice of the ancient Greeks.

In 1963, the Council of Europe established a definition of doping which the IOC slightly modified and adopted. It defined doping as "The administration of or use by a competing athlete of any substance foreign to the body or any physiologic substance taken in abnormal quantity or taken by an abnormal route of entry into the body with the sole intention of increasing in an artificial and unfair manner his/her performance in competition. When necessity demands medical treatment with any substance which, because of its nature, dosage, or application is able to boost the athlete's performance in competition in an artificial and unfair manner, this too is regarded as doping."

It is a definition that I happen to like, but a definition that has been abandoned.

According to the *IOC Medical Code* currently posted on the IOC web site, doping is presently defined as "the use of certain substances and methods intended to enhance and/or having the effect of enhancing athletic performance, such practices being contrary to medical ethics." However, like the banned drug list itself, the definition of doping is a moving target.

And speaking of lists, the banned drug list must be based on a generally recognized body of science, and where one does not exist, it must be based on some clearly reasoned rationale, including issues related to laboratory science. I am sure we would all agree that the current IOC list falls short in this regard.

Most recently, *the Olympic Movement Anti-doping Code*, as articulated in February of this year in The *World Conference on Doping* defined doping "as the use of an artifice, whether substance or method, potentially dangerous to athletes' health and/or capable of enhancing their performances, or the presence in the athletes' body of a substance, or the ascertainment of the use of a method on the list annexed to the Olympic movement anti-doping code."

It is a good thing we are holding this conference in a law school!

Although I personally prefer the first definition of doping that speaks of sole intent, it is still problematic. The linchpin of that definition is the notion that we can actually assess one's intent, both qualitatively and quantitatively

About intent, Peter Marc Latham in the early 1800s wrote: "Poisons and medicines are the same substance given with different intent."

Since there is no way to measure an athlete's intent, a surrogate measure, the testing of bodily

fluids, especially urine, has become a marker for assessing intent.

However, the neuro-chemical-biological pathways from what is on an athlete's mind, call it intent or call it artifice, to what comes out in his or her urine is tortuous and replete with physiologic treachery.

It has led to expensive and explosive litigation centered around the concept of strict liability, a subject I am sure we will hear much more about at this conference.

Creatine underscores a second problem when defining doping.

All would agree, that in recent years, the physiologic substance creatine has been taken in large amounts by an extraordinary large number of athletes, a process called creatine loading.

All would agree that at least in certain high intensity, short duration exercises, it enhances performance.

But, to date, there is no practical way to ban the practice and many would argue that beyond pragmatism, there is no definitional basis to ban it. Not only is creatine naturally produced by the body, it is widely found in a variety of food stuffs, such as meat and fish, thus raising the question: when is a physiologic substance considered to have been taken in abnormal quantity with the intent of gaining an unfair athletic advantage?

Employing urinary cut-off levels to eliminate its abuse remains a possibility. However, because creatine is so ubiquitous, the use of urinary cut-off levels probably would devolve into little more than an attorney's field day.

Inherent in any definition of doping is the notion that the technology exists that permits the definitive detection of substances foreign to the body or physiologic substances taken in abnormal quantity. Good luck!

Because advances in biotechnology have outpaced advances in laboratory science, the detection of certain drugs or biologicals is today either impractical or impossible. To wit, human growth hormone, erythropoietin and most recently, IGF-1.

IGF-1 is a polypeptide that is indirectly responsible for most of the growth-promoting effects of hGH. It is associated with a plethora of physiologic functions many of which are shared with hGH. These include increased protein synthesis, decreased protein breakdown and increased fat metabolism - all attractive to athletes.

Its approved uses in the united states are for a certain form of dwarfism and a rare form of insulin resistant diabetes. Like hGH, IGF-1 is not detectable with current screening methods and like hGH it needs to be administered intramuscularly.

One of the newer performance enhancing drugs, relatively little is known about its abuse patterns, cost, availability and long term side effects. The cost of IGF-1 is about $3 thousand per month and counterfeit products are problematic.

It is noteworthy that phase ii trials are currently underway utilizing a novel complex of IGF-1 and its major binding protein BP-3 to treat the degradation of muscles in a variety of medical conditions.

Those are some of the drugs we know but what about those we don't know? New drugs that are not listed. Hein Verbruggen, head of International Cycling Federation has suggested that "undetectable drugs are 90 percent of estimated doping cases."

We were told that in Atlanta, performance enhancing drugs would meet their match in high resolution mass spectrometry. And yes, it is an effective technique - but when investigators introduce something so new, it often takes a number of years for the technology to withstand legal challenges. To wit, O. J. And DNA. That's why the Atlanta games were clouded by the presence in the urine of the "new" stimulant drug, bromantan, and why political machinations resulted in five athletes being cleared of a doping offense by the on-site court of arbitration in sport.

Too often, it seems, we define international sports competitions and events, not by the city or country in which they were held, but by the drug that made the headlines - the Clenbuterol Olympics, the Bromantan Olympics, the Growth Hormone Games, the Steroid Pan Am Games, or the EPO Tour de France, or as some have suggested the Tour des Drugs.

There is good reason for this. If we look at the number and kind of new drugs that have come to market since the introduction of doping control in the Olympic movement in 1960s, the number is staggering.

This complicates life for every athlete who is faced with taking a drug or a biological substance for any reason whatsoever. He or she must first ask a series of questions: is it banned? Will it adversely affect my performance and is it safe?

Those determined to gain an unfair advantage will ask the additional questions: does it work? How does it work? Can it be detected during competition or out of competition, and perhaps, he or she might even be concerned about its long and short term safety?

That's today. But what about tomorrow? What is around the corner - brake drugs, blood substitutes, genetic manipulation? It is not a matter of a brave new world, but of brave new worlds.

Cyproterone acetate, also known as a Cyprostat and Androcur, is a synthetic steroidal anti-androgen and contraceptive hormone used in the treatment of prostate cancer in men, hair loss in women and precocious puberty in children.

Not available in the united sates, this so-called "brake drug" which has been associated with the development of liver tumors has allegedly become popular amongst female gymnasts because it puts the brakes on sexual development keeping the hips narrow and the breasts small.

And just as researchers are closing in on a method to detect the abuse of EPO, a potentially dangerous new EPO replacement, which is likely to increase endurance, has surfaced.

The substance is perfluorocarbon, or PFC, a substance with enormous oxygen-carrying capacity. It has been suggested that the abuse of this synthetic blood - like substance first surfaced in Nagano where it had been allegedly abused by cross-country skiers and speed skaters.

The International Cycling Federation has issued warnings about PFC to its national federations.

Although not officially on the market in the united states, there is active research into PFCs for legitimate medical use. PFC can significantly increase endurance by delivering more oxygen to working muscles.

With the global market for blood substitutes probably exceeding $2 billion, the number of new products will undoubtedly continue to grow. For example, active research is continuing using purified bovine hemoglobin rather than products of human origin or the use of PFCs to carry oxygen, and work continues on genetically engineered blood substitutes.

As we move into the next millennium, we are at the cusp of gene therapy for the correction of defective human genes that cause or promote certain genetic diseases, and designer genes cannot be far behind. Human skin has already been genetically engineered.

Combining cloning with genetic engineering, so called germ line therapy, will make possible the passage of genetic changes from one generation to the next.

It was only six months ago that scientists achieved one of the most coveted goals in biology, isolating from human embryos, a primitive cell, called a pluripotent stem cell, that can grow into every kind of human tissue, including muscle, bone and even brain.

Already stem cells have been used to grow human heart muscle cells which beat in unison in a petri dish, as well as nerve cells, bone, cartilage and skeletal muscle. To insure that stem cell research is conducted in an ethically sound manner, just last month, an NIH special working group was formed by the director of the NIH to develop research guidelines.

If this sounds like the twilight zone, think twice. Only five months ago, researchers at the University of Pennsylvania discovered a form of gene therapy to counter muscle degeneration associated with aging.

The injection of this gene limits the effect of IGF-1 to the skeletal muscles into which the gene is directly injected obviating any adverse effects of IGF-1 on the rest of the body.

With this technique young mice experienced a 15% increase in muscle strength, and old mice a 27% increase. Accordingly, the gene has been dubbed the "fountain of youth" for skeletal muscles.

But in the world of doping, milestones become millstones.

The author of the original study has already expressed concern that this technology may be sought out by athletes who are seeking a competitive edge. Interestingly, muscle strength increased without any exercise and there was no way to detect the use of gene therapy from analyzing the blood.

Trials are to begin in monkeys and, in the not too distant future, the first human study may be done in people with a form of muscular dystrophy.

And in another study, IGF-1 producing genes have been successfully introduced into mouse embryos. Is it a stretch that with the new technologies of genetic engineering that we are arming parents with the tools to create designer offspring whether inside the uterus or out of it?

Of course, the ethical, moral and biological debate transcends sports. Indeed, it touches on the transcendent as George Wald, the Nobel Prize-winning biologist and Harvard professor, opined: "Recombinant DNA technology (genetic engineering) faces our society with problems unprecedented not only in the history of science, but of life on earth. It places in human hands the capacity to redesign living organisms, the products of some three billion years of evolution".

We stand at the brink of an uncertain future. But I personally believe that the unpredictability and the velocity of change are not an excuse for reserving judgment about some profound distinctions that should fundamentally govern our perspective on the role of sports in our social fabric.

With that in mind, I would like to conclude by quoting the columnist George Will who reminds us: "A society's recreation is charged with moral significance. Sport - and a society that takes it seriously - would be debased if it did not strictly forbid things that blur the distinction between the triumph of character and the triumph of the chemistry."

And finally, in order that we not blur the distinctions George Will speaks of, what we must do in this complex and challenging environment, is confront the issues related to doping from the broadest possible perspective.

Tempting as it is to get consumed by the intricacies of anabolic steroids, EPO or hGH, I urge you to think expansively and inclusively, to keep the big picture in mind, and to maintain an aerial view, for these drugs are only specific examples that stretch along the continuum from strychnine

to genetic engineering.

Only in that way can we hope to forge a consensus, a unified, expert-wide point of view that will help us put the details and the subtleties in proportion.

Stay tuned.