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REVIEW ARTICLE

Doping yesterday, today, tomorrow: A challenge for the clinical laboratory

Roberto VERNA

Department of Experimental Medicine, Sapienza University of Roma, Italy

Abstract

This work highlights the role of the clinical laboratory, in the early detection of the use of substances prohibited for doping. This is because most people who practice sports today are non-professional athletes and amateurs, in particular young kids. These persons are not subjected to anti-doping controls but are at risk for their health. Endocrinologists and laboratory tests, by detecting evidence of such usage can help protect their health. Anti-doping testing require specific instruments for qualitative and quantitative chemistry, to meet regulations of official competitions but are impossible to be used in every person because of high cost. A particular role the clinical laboratory can acquire in the future is through its molecular biology sections, when genetic doping will probably be a reality and quantitative chemistry will be unable to detect it. A brief history of doping is provided to understand the reasons of its spread. Although doping has great resonance nowadays, it is not a recent problem. It was common among ancient Greek wrestlers and Romans, who used mixtures of herbs and stimulants. Ancient Greece started the Olympic Games and winners assumed great esteem, akin to demi-god status. Therefore, any attempt to improve athletic performance was a norm, also because the damage caused by the substances used was not known at that time. The use became so widespread that soldiers also used drugs to better combat during recent wars, and doping was practiced by athletes, actors and musicians in attempts to obtain better performance results. Today, doping has been refined so as not to be discovered and there is a continuous race between those who promote new substances and those who, like the World Anti-Doping Agency (WADA), were created to defend the health of athletes and comply with regulations of competitions. The clinical laboratory plays a fundamental role in identifying the use of prohibited substances, especially in competitions not classified as official, which are the majority and involve thousands of amateurs. In this paper a series of laboratory tests are proposed in this perspective, at low cost without the need of qualitative/quantitative chemical analyses required by the sport jurisdictions. Finally, a glance into genetic doping illustrates a likely future and imminent practice.

INTRODUCTION

As early as the 18th century, sports medicine has been dedicated to the study of the pathophysiology of athletes and how to increase their performance.[1] Through the last half of the twentieth century, as exercise became more central to public health, the medical community began to view exercise as part of lifestyle.[2] Sport has changed over time, and the need for notoriety and financial aspects linked to success have surpassed the importance of the athletic result.[3] The laboratory has demonstrable importance in the evaluation of the athlete and in the prevention of any physical damage.[4]

In analogy to what occurs in car races, where the manufacturers develop engines, braking systems and suspensions to be used in commercial cars, with sports, the laboratory has the possibility of establishing reference parameters in people young, healthy, and in good physical shape. These parameters may then be used as reference to define deviations from the state of well-being. Physical exercise induces adaptations in metabolism considered beneficial for health. Athletic performance is linked to adaptations: training, and correct nutrition in individuals with genetic traits that can facilitate such adaptations. Intense and continuous exercise, training, and competitions, however,

**Address for correspondence:* Professor Roberto Verna, Department of Experimental Medicine, Sapienza University of Roma, Viale Regina Elena, 324, 00161 Roma, Italy. Email: *roberto.verna@fondazione.uniroma1.it*

can induce changes in the serum concentrations of numerous laboratory parameters.[5] Sport is also of great importance for the physical and psychological growth of children. In Italy, around one million non-professional football matches and a myriad of events organised by municipal administrations take place every year.[6]

What about doping? What is it? Italian law has defined doping as follows:
"Doping is the administration or assumption of drugs or biologically and pharmacologically active substances and the use of medical acts without any need justified by pathological conditions and able to modify physical or biological conditions in order to achieve the best performances by the athletes".[7] The name seems to have come from the Dutch "doop" - a mixture used by Dutch sailors to overcome their fear of severe storms. Hence the term Dope and finally Doping. But there is also another possible origin: oop or the South African term dope. In any case, doping implies cheating and cancels the values of sport, in which to win, you must train and strive to achieve the result.

There are three types of doping, related to different moments of the agonistic activity: (1) before the match, during the training, in order to increase muscular mass and physical strength or resistance (steroids – Epo); (2) after the match, to rapidly recover strength; (3) during the match to decrease fatigue, stimulate the central nervous system, to reduce anxiety (cannabinoids, beta blockers), to increase oxygen transport and reduce fatigue (haemotransfusion). Sport authorities are bound to protect the athletes' health, enforce medical and sports ethics and maintain the same opportunities for all athletes during a competition. The use of prohibited substances is an admission of fear and inability to accept defeat. It is also a path to drug-addiction.

Yesterday

Even though doping has great resonance nowadays, it is not a recent problem, but an ancient one. It was common for Greek wrestlers to use a mushroom derived drug to enhance their aggressiveness. Romans used mixtures of herbs and stimulants.[8]

To understand how important victory was at that time, one must remember that victory at the Olympics made the winner a demi-god and conferred great power. A notable example is the story of Kallipateira of Rhodes. Kallipateira wanted to watch her son's fighting and disguised herself as a man because at that time women were forbidden to attend. When her son won, throwing himself on the stage, the peplos opened showing her real nature. The penalty was death but because she was the daughter of an Olympic champion and sister of two Olympic champions, as well as now the mother of an Olympic champion, the sentence was annulled.[9]

Another pertinent story is the famous race of Philippides to announce the victory of Marathon, but few people knew that prior to that, Philippides had first run to Sparta to request for help in the battle, and upon victory he ran to Athens to announce it. To run all those kilometers he assumed a great feat, so much so that he died upon arrival.

However, Philippides was not alone in such feats; the unfolding of the battle of Marathon bears witness to this. The Battle of Marathon was fought in August or September 490 BC, in the context of the first Persian war and saw the forces of the polis of Athens, supported by those of Plataea and commanded by the polemarch Callimachus, opposed to those of the Persian Empire, commanded by the generals Datis and Artaphernes. The origin of the conflict lay in the military support that the Greek poleis of Athens and Eretria had provided to the Hellenic colonies of Ionia when they rebelled against the empire. Determined to punish them harshly, King Darius I of Persia organised a military expedition in 490 BC. Having subdued the Cyclades islands and reached the island of Euboea by sea, the two Persian generals Datis and Artaphernes landed a contingent which besieged and destroyed the city of Eretria. The fleet continued towards Attica, landing on a coastal plain near the city of Marathon. Learning of the Persian landing, the Athenian forces, together with a handful of hoplites from Plataea, hurried towards the plain with the intent of blocking the advance of the larger Persian army. Once they decided to give battle, the Athenians managed to encircle the enemy who, in panic, fled in disorder to the ships, thus decreeing their own defeat. Having re-embarked, the Persians circumnavigated Cape Sounion, planning to directly attack undefended Athens. But the Athenian army, led by the strategist Miltiades, rushing towards the city with forced marches, was able to foil the Persian landing on the coast near Piraeus. Once the surprise failed, the attackers returned to Asia Minor with the prisoners captured in Eretria.

If we think about the battle-map, we wonder how it is possible that an army on foot could have arrived before a naval fleet, even with a reduced

distance. It is probable that the widespread use of substances played a strategic role.[10-12]

The tale of Philippides' feat has endured over the centuries to inspire the conception of the marathon foot race, which in 1896 was introduced into the official program of the first edition of the modern Olympic Games held in Athens. For curiosity, the distance of 42 km was increased to 42.195 km in order to finish in front of Buckingham Palace in the London Olympics in 1908.

Even the battle of Thermopylae saw 300 Spartans resist a million Persians: great strategic positioning, but also huge amounts of stimulants to not feel fatigue. The epic battle is remembered today with a mausoleum.[13,14]

During those times, the Olympic Games were alight with magical practices, feasts and drugs, so much so that the emperor Theodosius, at the express request of Sant' Ambrogio in 392 AD suspended the games. It resumed in 1902 thanks to Baron De Coubertin.[15]

Today

The history of doping resumed at the end of 19th century. Arthur Linton, Thomas Hicks and Dorando Petri were the most famous case names of doping.[16-18]

Arthur Linton, an English bicycler, won the Paris-Bordeaux in 1896, dying after the race because of the use of exciting substances (ether-cocaine). In 1904 Thomas Hicks, after winning the Olympic marathon in Athens, was taken seriously ill due to the use of stricnine sulfate during the race. Dorando Petri upon his marathon race completion (London 1908) was worn-out by fatigue because of the intake of stricnine with cognac.

Doping has the purpose of increasing performance. This does not happen only in sports. Magicians and Secret societies made use of it to surprise the participants. Furthermore, a large number of artists is reported to use drugs, sometimes with fatal outcome. Famous examples are Kurt Kobain, Jim Morrison, John Belushi, Jimi Hendrix and many others.

On the other hand, it is true that until about forty years ago, heroin-based syrup was available in pharmacies to relieve cough (Glyco Heroin Smith). Even the armies needed "help". During war, landings, air strikes and missions in the desert, were aided by massive doses of amphetamines and other drugs, in order to maintain high attention.[19-21]

Anti-doping was born in Rome in 1960, when Knud Enemark Jensen, a Danish cyclist full of amphetamines, had not considered that in August on the Rome Ostia race, the temperature could increase over 40°C. He was taken ill and died. The cycling federation then set up the first anti-doping laboratory in Florence, which is now located in Rome. Eastern European countries (primarily the German Democratic Republic) were forerunners in systematically applying doping from the 1950s to the 1980s, especially on athletes taking part in the Olympics.[22] Further developments followed after the case of the Canadian sprinter Ben Johnson (at the 1988 Seoul Olympic Games) and the end of the Cold War in 1989, when the world political authorities, urged by the International Olympic Committee, created on November 10 1999, the World Anti-Doping Agency, which launched the WADA World Anti-Doping Code which was then accepted by national sports federations.[23] The seriousness of the problem came to light during a series of police operations in the early 2000s (Tables 1 and 2). The World Anti-Doping Agency establishes the list of prohibited substances and methods, which is updated every six months.[24]

But why do athletes use drugs? Since the differences in the athletes' performances from training are marginal, any kind of help that can improve performance is sought. A survey of 8,000 athletes showed that 60-70% use drugs, even if they are not prohibited.[25] Furthermore, the use of various types of supplements is very widespread, many of which are herbal, and these herbal products do not exclude that they may contain prohibited substances.[26,27]

What are effects of doping substances and, above all, their adverse effects and damage to health? The list of prohibited substances is published by WADA each 6 months or at least once a year.[28] Tables 3 to 6 list the prohibited subtances and methods. Furthermore, as previously mentioned,[26,27] great attention should also be paid to supplements, many of which are not safe.

The challenge of the clinical laboratory

Official sports events, those organised by the Federations, in which any eventual achievement record must be confirmed and made official, are subject to anti-doping controls. Since sports justice must be rapid, especially in international events such as the Olympics or world championships, it is essential to identify the substance taken and in what quantity,

TABLE 1: List of the substances found during confiscation (police operations)

ALDACTONE	LASIX	RESTANDOL
ANAPOLON TABLET	HOMEOCUR TESTERSET	SAIZEN
OKSIMETOLON	HUMOLIN	SCHERING
ANDRIOL	JINTROPIN	SYNFLEX
BENADON	KADIUR	SOMATOSTATINA
CLOMIPHENE CITRATE	KRIPTOCUR	SPASMOBRONCAL
DECA-DURABOLIN	ISOPURAMIN	SPIROPENT
DIANABOL	LIPOSTABIL	SUSTENON
DEPO MEDROL	MASTERON	TAD 600
EFEDRINA LEVEL	METADIENON	TIOSIDE
EPARGRISEOVIT	METANABOL	TI-TRE LIOTIRONINA
ESICLENE	MONORES	TESTEX ELMU
ESTRUMATE	NAPOPSIN	PROLONGATUM
EUTIROX	NEOTON	TESTOSTERONE
EXTRABOLINE	NESPO 60	CYPIONATE
FELDENE	NOVALDEXTAMOXIFEN	TESTOVIRON
FINAJECT	PARABOLAN	TESTOVIS
FINASTERIDE	PLACENTEX	TRANSMETIL
GANABOL	PRIMOBOLAN	VENTIPULMIN CITRATE
GENOTROPIN	PROFASI HP	VIRORMONE
GH UMATROPE	PROCAR FINASTERIDE	TESTOSTERONE
GLOBUREN	PROVIRON	PROPINATE
		WINSTROL

TABLE 2: Jargon words used to order drugs, recorded during tapping (police operations)

EPHEDRINE	Mau-Wang
WINSTROL	double U - dresses- STROMBA
GANABOL	(for veterinary use)
DECA	“the ones with the yellow cap”
	masterized
ANDRIOL	the moto
DECADURABOLIN	the cars
NANDROLONE DECAONATO	lat extension
PROVIRON	
OXANDROLONE	trousers
HASHISH	lat machine
GH	smoke – chocolate
	“the cold one” the ice – frozen proteins
	chewing gums
PRIMOBOLAN	P – decaffeinated
PROVIRON	PRO
TESTOVIS	“those with the blue box”

rapidly. Therefore, doping controls are based on qualitative/quantitative analytical chemistry, using instrumentations such as gas-mass spectrometry. The cost of these tests is quite high and is routinely supported by the sports federations, which indicate how many checks to perform. It is therefore obvious that richer federations are able to carry out more controls.

The clinical laboratory does not use such equipment, apart from unusal clinical cases, where the cost is justified by a particular diagnostic suspicion, such as the use of HPLC or Gas-Mass spectrometry for the detection of catecholamines. It would not be able to bear the

TABLE 3: Classes of substances prohibited only in competition

Stimulants
Narcotics
Cannabinoids
Glucocorticoids

Table 4: Classes of substances prohibited in and out of competition

Anabolic Agents
Diuretics and Masking Agents
Peptide Hormones
Beta-2 Agonists
Antiestrogenic Agents

TABLE 5: Classes of substances prohibited only in some sports

ALCOHOL	BETABLOCKERS	
Aeronautics	Aeronautics	Football
Archery	Archery	Gymnastic
Motoring	Motoring	Modern Pentathlon
Billiards	Billiards	Motorcycling
Bowls	Bobsleigh	Bowling 9 pins
Football	Bowls	Sailing
Gymnastics	Bridge	Shooting
Karate	Chess	Ski
Modern Pentathlon	Curling	Swimming
Motorcycling		Wrestling
Skating		
Ski		
Triathlon		
Wrestling		

Table 6: Methods always prohibited

ENHANCEMENT OF OXYGEN TRANSFER • Blood doping: use of autologous, homologous or heterologous red blood cell products of any origin, outside of legitimate medical treatment • Use of products that enhance the uptake, transport or delivery of oxygen (eg erythropoietin), hemoglobin products, including but not limited to hemoglobin-based blood substitutes, microencapsulated hemoglobin products, perfluorochemicals, and efaproxiral (RSR13)
DRUG, CHEMICAL AND PHYSICAL HANDLING • Use of substances and methods that can alter the integrity and validity of specimens collected in doping controls (intravenous infusion, catheter and replacement of urine)

costs of sports doping testing, given that clinical analyses are paid for by the National Health System (where applicable) or by the insurance companies.

And so the challenge lies in identification as soon as possible, through the routine tests of the clinical laboratory, for signs and markers of the possible use of substances prohibited for

doping. This is of particular importance, given the large number of young people who engage in sports as amateurs, and are not subject to doping controls but are at high risk of taking harmful substances. We have seen how the vast majority of sporting events are not official ones and therefore the participants in these events are not checked. The issue here is not mandated by the regulatory requirements of competition, but to protect health and in this, the clinical laboratory has an enormous role, through the highlighting of markers that can reveal the use of substances that are prohibited because they are harmful.[29]

Laboratory tests are capable of revealing the possible use of prohibited substances, through the effects that occur in the peripheral blood, and thus can be very useful in sports medicine to monitor the physical state of athletes (Tables 7 to 12).

Tomorrow

The new frontier is genetic doping. This is based on the manipulation of genes, using the results obtained in gene therapy. It is a future threat for athletes. The purposes of gene therapy are: to kill or weaken cancer cells; making the body to reproduce substances now available only on

Table 7: Markers utilised by the clinical laboratory

Haematochemical markers of the physical condition of the athlete. Evaluation of the agonistic stress and involvement
Testosterone
Diidrotestosterone
ACTH
Cortisol
DHEAs
delta-4-androstenedione
GH
Study of the muscular characteristics of an athlete
LDH
CPK
Mountain Sports
Complete Blood Count
Iron
Transferrin
Ferritin
Hb dissociation curve
Diphosphoglycerate

Table 8: Clinical signs of the use of anabolic agents and analytes useful to reveal their use

Increased muscle mass	FSH	↓
Reduced body fat	LH	↓
Reduced resistence	PT	↓
Increased aggressiveness	PTT	↓
Increased catabolic action of glucocorticoids	Tot. Chol.	↓
Increased synthesis of red blood cells	HDL Chol	↓
Increased bone density	GH	↓↑
These signs are accompanied by haematochemical	CPK	↑
alterations	AST - ALT	↑
Increased haematocrit	LDH	↑
Increased number of platelets	Testosteron	↓
Reduced levels of FSH and LH	Estradiol	↓
Reduced testosterone levels	Estrone	↓
Reduced HDL and Total Cholesterol		
Increased glycemia and Insulinemia		
Increased liver enzymes and indices of cholestasis	*Legend: ↓-decrease; ↑- increase;*	

TABLE 9: Tests to reveal the use of corticosteroids, narcotics and analgesics

Blood glucose	LH
Blood potassium	ADH
Blood pH	GH
	Prolactin
	Testosteron

TABLE 10: Tests to reveal the use of EPO and analogues

Peripheral blood examination including RBC indices
Reticulocytes ↑
Transferrin ↑
Ferritin ↑
Folic Acid =
Vitamin B12 =
Iron ↑
CD 71
Glycophorin A
Bilirubin
CFU-E
BFU-E

TABLE 11: Tests able to detect the use of GH

GH
LH
FSH
Cholesterol
TG
Creatinine Clearance
BUN
Glucose
IGF-1
IGF- BP2
IGF – BP3
NEFA
Insulin

TABLE 12: Tests able to detect the use of diuretics

Na
K
Cholesterol
Ht
Plasma and Urine electrolytes
17-OH corticosteroids
Urine pH (or blood)
Uric acid
Urinary Glucose
Urinary aldosterone
Na, K Pump
Na, K Cotransport

administration and; replace defective genes with healthy copies. Genes are introduced by direct injection, by injecting cells or by means of a viral vector[30-32] (Fig.1). Another example is the use of growth factors to increase muscle size (Fig.2). Another important mechanism is removing the gene that controls the growth of muscle mass (myostatin) (Fig. 3).

Finally, the last example is from one of the first human experiments with gene therapy.[36] In this case the VEGF hormone is used to induce growth of blood vessels in patients suffering from critical lower limb ischemia due to impaired blood flow. These patients have severe tissue death in the extremities due to the lack of sufficient oxygen supply. As seen from Figure 4, the treatment worked. In figure B, new blood vessels were formed and the blood flow increased.

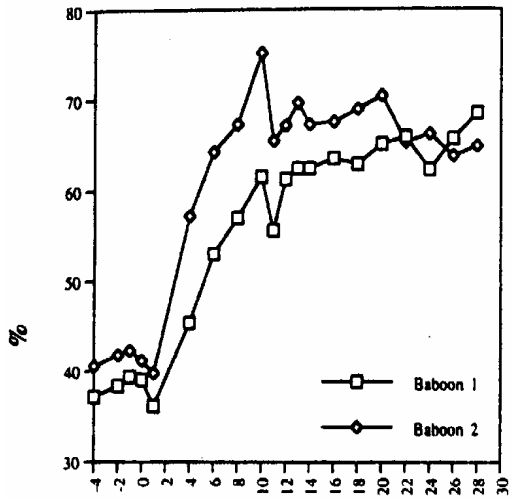

FIG. 1. Effect on monkeys inoculated with a virus carrying the gene for EPO. Reproduced from Zhou *et al*.[33]

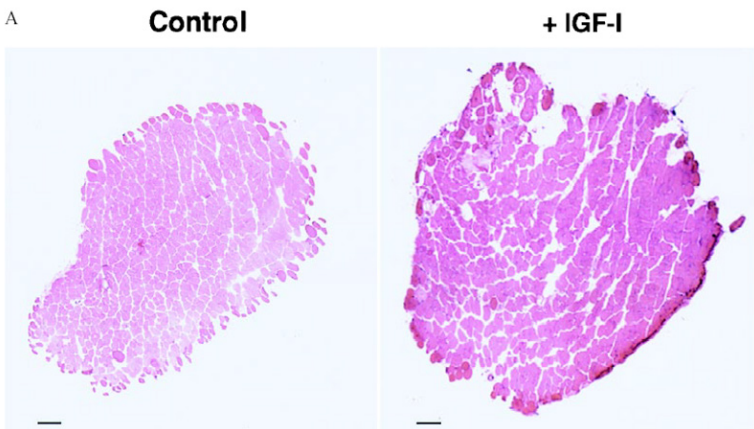

FIG. 2. Mice injected in the muscle with the IGF-I gene resulting in increased size and strength of the muscle. Reproduced from Barton Davis *et al*.[34]

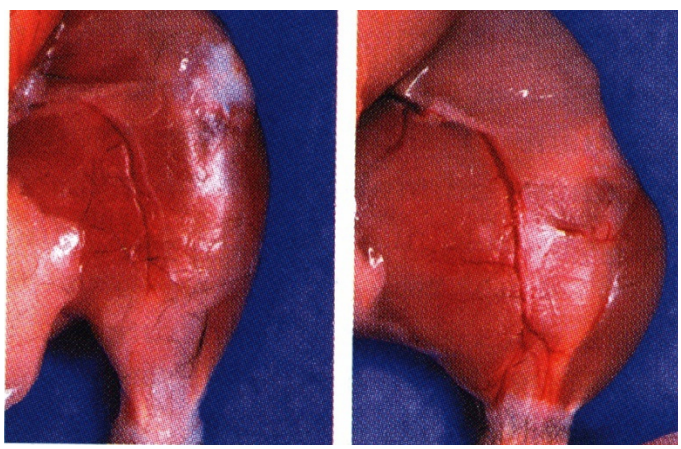

FIG. 3. Increase in muscle mass (right picture) after removal of controlling gene. Reproduced from Lee *et al*.[35]

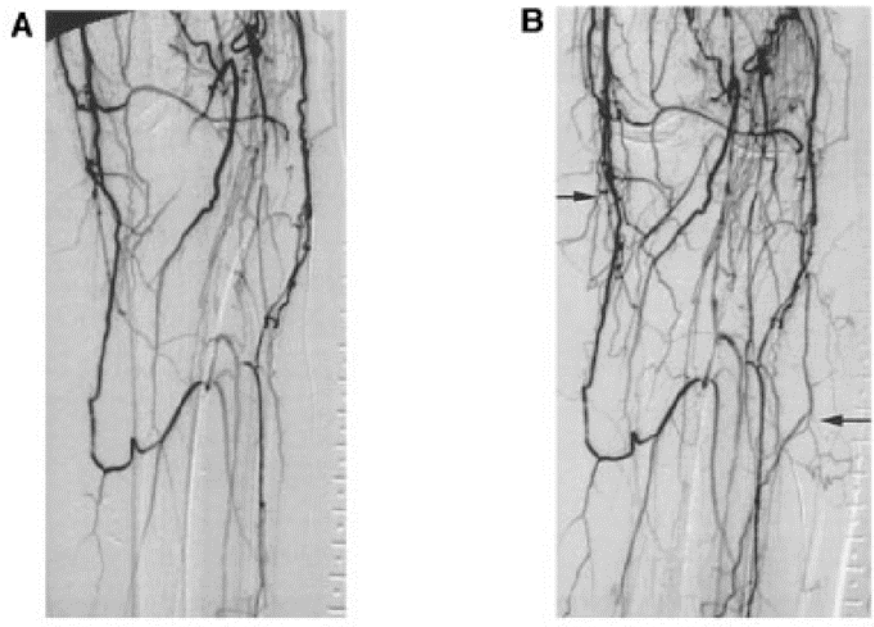

FIG. 4. Increase in vasculature (B) induced by VEGF hormone. Reproduced from Baumgartner *et al*.[36]

Many of the physiological effects of GH are mediated by the production of insulin-like growth factor-I (IGF-I),[37] so that both GH and IGF-I appear on the World Anti-Doping Agency list of prohibited substances.

Can we discover gene doping? This is a particular opportunity for the clinical laboratory, mainly its molecular biology section, to overtake the anti-doping laboratory. In fact, the quali/quantitative methods used by the anti-doping laboratory are almost unuseful in detecting gene doping.

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