

Towards the perfect human machine?

Doping & society

Barcelona on 21 July 2008- In the current setting of the imminent Peking Olympic Games, the fight against doping takes on particular relevance and lets us tackle concepts like the limits of the human body, physical resistance, sport ethics and doping as a means to obtain eternal fame and glory, an idea that arose in Greece over 2000 years ago.

With this objective, next **Tuesday 22 July** at 14:30, in the framework of the Euroscience Open Forum (ESOF 2008), the session '*Doping and society: towards the perfect human machine?*' will be held, organised by **Dr Jordi Segura**, director of the Anti-doping Laboratory of the Municipal Institute of Medical Research (IMIM-Hospital del Mar) in Barcelona and member of the Medical Commission Games Group of the International Olympic Committee (IOC). Internationally renowned experts will also be present such as **Dr Alain Garnier**, medical director of the World Anti-Doping Agency (WADA), **Dr. Franchek Drobnic**, Physiology Department, High Performance Centre (CAR), **Dr Michele Verroken**, director of the Sporting Integrity consulting agency based in London and former manager of UK Sports, **Xavier O'Callagan**, former handball player for FC Barcelona and current manager of the handball department of FC Barcelona and **Dr Francesco Botré**, former president of the World Association of Anti-Doping Scientists (WAADS) i scientific director of the Anti-Doping Laboratory in Rome. **Mr Josep Guardiola** will also participate through a pre-recorded statement, a former player on FC Barcelona and the current coach of its 1st team.

According to Jordi Segura '*Doping is dangerous to the ethics of sport itself and to the health of athletes. As fans, we must get used to not expecting stratospheric records so often and enjoy fairer and more balanced sport*'. Despite the fact that anti-doping laboratories estimate that only between 1 and 2 % of athletes use drugs, the high risk of this practice to athletes' health is clear, which in some cases have even led to death. We must remember though that the athlete is almost never the only guilty party, since modern doping takes place in an organised setting that incites and provides athletes with the illegal means necessary.

In recent years, the scenario has changed from a fight against classic doping where the substances used -stimulants (amphetamines, etc), narcotics (methadone, morphine, etc), anabolic steroids (testosterone, Estanozolol, etc)- were easily detectable, to doping based on stimulation of the growth hormone or the supplying of erythropoietin, products generated by the body itself, a fact that complicates the analysis and interpretation process of the results. Furthermore, in the near future, specialists forecast that new and increasingly sophisticated methods will have to be dealt with, such as genetic doping.

Society must be aware that media, economic and social prestige of being the winner of important competitions will continue stimulating the temptation to employ illegal practices to obtain this goal and, therefore, it is very difficult to definitively eliminate the problem, above all in individual sports where results depend on the strength and resistance of one person. However, it does seem possible to control the situation within certain limits that allow faith in clean sport practices to be maintained.

All of these issues will be debated at the session on the 22nd, with the aim of providing a general overview of the fight against doping from different viewpoints: scientific, institutional, ethical and the viewpoint of the athletes themselves. Special emphasis will also be placed on the future development of anti-doping control from the perspective of scientific laboratories, in the context of clean play and health protection.

Press conference:

Day: 22 July at 13:15
Location: Press Room, Hall 5, level 2, room 7
ESOF 2008

Doping: towards the perfect human machine?

In a society where sports success provides fame, glory and money, managing to be the best at any price is a great temptation that can lead to employing prohibited substances and/or methods. Under this premise, international experts from anti-doping bodies, organisations that manage controls, associations of scientists interested in the issue and the athletes themselves will participate in this scientific session that will discuss the situation of doping in sport at a time of special significance, right before the Peking Olympic Games.

An international multidisciplinary vision

The scientific session is organised by Dr Jordi Segura, at which international experts in the field of doping and sport will also participate.



Jordi Segura, Director of the Anti-Doping Laboratory of the Municipal Institute of Medical Research (IMIM-Hospital del Mar)

He is also the coordinator of the research group of Bio-analysis and Analytic Services of the Neuropsychopharmacology Research Programme at IMIM, member of the Medical Commission Games Group of the International Olympic Committee (IOC) and of the Doping Control Review Board of the International Swimming Federation (FINA). He is an expert in chromatography, mass spectrometry and hormone analysis. Finally, he is a tenured professor in the Department of Experimental and Health Sciences at the Pompeu Fabra University.

The Anti-Doping Laboratory of the Municipal Institute of Medical Research was created in 1985 and is accredited by standard ISO 17025 and the World Anti-Doping Agency. It was the laboratory responsible for anti-doping control during the 1992 Barcelona Olympic and Paralympics Games. Later, the laboratory has also controlled large international events such as the 1991 and 1995 Pan American Games, the 1998 Asian Games and the 2003 World Swimming Championships, among others. The laboratory receives samples and consultations from around the world each day.

Dr Jordi Segura, under the title: '*Doping and Society: towards the perfect human machine?*', which also gives its name to the entire scientific session, will give us a general introduction about the current state of doping and its control and will offer us a summary of the forecast for the near future.



Alain Garnier. Medical Director of the World Anti-Doping Agency (WADA-AMA)

He embarked on his career with WADA as a medical consultant in 2000, thanks to his prior experience as a sport specialist doctor for several French hospitals and head of the medical division of the French Ministry of Youth and Sport. In the framework of WADA, he was a member of the group that developed the World Anti-Doping Code (Code) and one of those in charge of assuring the code's acceptance by different governments. He is currently the medical director of WADA, in charge of all medical issues related to doping, especially the supervision of the

Therapeutic Use Exemptions programme and the WADA Athlete Passport project.

Under the title: '*Moving from toxicology to biology: the need for a medical approach in the fight against doping*', Dr Garnier's paper will give us a medical approach to the current situation of the fight on doping. Why must sport doctors oppose doping? Are there long-term health consequences? Can restricted substances be taken if there is no alternative pharmacological alternative? Special emphasis will be paid to the impact in the Therapeutic Use Exemption (TUE) process and the idea of the Athlete's Passport. The aim of the latter is to carry out a longitudinal monitoring of the biological parameters of athletes, an initiative that will permit the identification of abnormal profiles for the use of prohibited substances or methods.



Michelle Verroken, Director-founder of Sporting Integrity

The Sporting Integrity consultancy was created in 2004 and is the first and only of its type in the United Kingdom. Its aim is to advise its clients about good sport practices and to adopt and maintain the best procedures related to sport ethics and integrity.

Mrs Verroken has two decades of experience as a world expert in the field of ethics and sport. Director of Ethics and Anti-doping at UK Sport, she was responsible for designing and implementing the internationally accepted standards for anti-doping control, results management and education, in addition to creating the UK Drug Information database and national anti-doping policies (on which the World Anti-Doping Code is based).

Under the title: '*Ethics and Doping- ethos, pathos or kudos?*' Mrs Verroken will speak about clean sport ethics and the need for all of us to be aware of the importance of this control. According to Verroken, the rules of the game should be the essence of sport. Sport's corruption through doping is destroying this sole ethical principle. Athletes often become the interpreters, who are trained using training systems that use the latest scientific innovations. Drawing the line between what is acceptable and unacceptable is becoming increasingly difficult. She will exemplify this complex issue with specific and illuminating experiences.



Franchek Drobnic. Director of the Physiology Department at the Olympic Training Centre (CAR) in Sant Cugat.

He is a doctor of medicine, licensed from the Autònoma University of Barcelona, and is a specialist in Sports Medicine. He is the current director of the Physiology Department at the Barcelona Olympic Training Centre and director of Medical Services for the Spanish Federation of Taekwondo. He also collaborates directly with various sports in preparation for the Olympics.

His interest as a researcher in the sports world is broad and is oriented towards improving athletic performance through health, with a special emphasis on respiratory disorders and adaptation to physical stress, as well as on the physiology of physical performance and reparatory physiology under special conditions, such as the exercise itself, hyperbaria, hyperoxia, changes in temperature or the state of hydration and nutrition.

His presentation "*Therapeutic Use Exemptions: why and when?*" will describe the possibilities for administering prohibited products to those affected athletes who need them. In its two versions (conventional and abbreviated), "*Therapeutic Use Exemptions*" will provide the relevant medical information for the use of these medicines in pathological situations where there are no other alternatives. The presentation will highlight some of the most common therapeutic use requests, such as those related to athletes with asthma or exercise-induced asthma.



Xavier O'Callaghan, former handball player on FC Barcelona and current manager of the handball division of FC Barcelona

He entered the lower categories of FC Barcelona, winning three state youth and one junior championship. In the 1990-91 season, when he was 18 years old, he moved to the first team, on which he would play for 15 seasons. He is one of the athletes who has won the most state and European titles (54). He played internationally 87 times and scored 140 goals, as well as winning a bronze medal at the 2000 Sydney Olympic Games and an Olympic title at the 2005 Athens Games. At the end of the 2005 season, and after an entire career with FC Barcelona, he became the manager of the handball division of FC Barcelona.

His presentation will present his vision of doping both from a viewpoint as an athlete and as a sport manager. From his personal vision and based on his sports experience, Xavier O'Callaghan will try to answer the question of why there are athletes who use drugs and others who choose not to and what factors can influence this decision.



Francesco Botrè, former president of the World Association of Anti-Doping Scientists (WAADS) and director of the Anti-doping Laboratory in Rome

Dr Botrè is an associate professor at the Sapienza Faculty of Medicine at the University of Rome, a member of the WADA laboratory work group and the Medical Commission of the International Committee for the Mediterranean Games. He is also a member of several scientific societies, the author of over 200 scientific publications, conference papers and monographic works.

His presentation '*Testing: scientific aspects. Who are the laboratory experts?*' will speak of the activities performed at anti-doping laboratories that WADA-accredited; carrying out a study on the evolution they have followed in recent years to become more effective in the fight against doping. He will place special emphasis on the future evolution of doping science, taking a position that is pro fair play, health protection and society's knowledge of the work done at an anti-doping laboratory.



Josep Guardiola, former football player and current trainer of the first football team of FC Barcelona

He has been one of the most important midfielders in Catalan football. He played 43 times with the Spanish team and was the captain of the Catalan team for many years. In 2001, he started playing on Brescia and a mere two months later was accused of doping by the Italian National Olympic Committee. It was not until 2007, six years later, that the Brescia Court of Appeals absolved him when new scientific proof appeared that explained

the natural origin of the tests. He is now the trainer of the first team of FC Barcelona.

His participation will be done via a pre-recorded statement since at the time of the session he will be out of the country. He will give his personal viewpoint on doping. The priority issues that he will discuss are his vision of doping and its control from a sport perspective, the role that can be played by the environment closest to athletes, his own experience due to being suspected of doping, some considerations about the future of the anti-doping fight and what role science can play in the improvement of controls.

The origins of anti-doping control

The use of substances or other methods to improve performance is as old as competition sports. It is known that the athletes who participated at the Olympics in Ancient Greece (4th-8th century AD) employed special diets and stimulating potions to enhance their capacity. Moreover, it was not until the beginning of the 20th century that the need to control the usage of doping substances in sport was considered. Initially, there were no means for detecting the use of these substances, but scientific advances led to the instauration of progressive anti-doping controls starting in the sixties by the International Olympic Committee and the main sports federations. Unfortunate events like the death of some cyclists revealed the initial use of amphetamines and narcotics. Subsequently, the increasing use of testosterone and its derivatives (anabolic steroids) came to light as doping elements. The current list of substances includes many other pharmacological groups. The biotechnological revolution in medicine has also had a phenomenal effect on the consumption of doping substances with an identical structure to those produced by the human body. The upcoming arrival of genetic doping will add further complexity to the ethical aspects and detecting of doping in the future.

Present-day doping

Present-day doping products and methods

Every year, WADA makes a list of prohibited substances. You can see the most updated list on its Web page at <http://www.wada-ama.org>. These substances are broken down into large categories such as anabolic agents, hormones and related substances, stimulants and narcotics, to name just a few examples. It also includes a list of prohibited methods, which include increased oxygen through transfusion (blood doping), chemical or physical manipulation, meaning the handling or replacement of samples or genetic doping.

Performing anti-doping controls for the components on the list is very technically complex, expensive and can only be done at 34 laboratories in the entire world, those accredited by WADA, including the Barcelona Anti-Doping Laboratory of the Municipal Medical Research Institute (IMIM-Hospital del Mar).

We include a chart hereafter with some examples of prohibited substances and their effects on sport performance and side effects with regard to health.

PROHIBITED SUBSTANCES (some examples)	EFFECTS	SIDE EFFECTS
Substances that increase the quantity of oxygen in muscles		
Erythropoietin (EPO)	Increase in red cells and increased oxygenation and resistance	Serious cardiovascular problems
Darbepoetin	In the EPO family, but lasts longer in the blood	Cardiovascular problems
Insulin	Very important in transporting nutrients to cells, permitted in diabetics	Cardiovascular problems and diabetic coma
Blood transfusion	Very effective in quickly improving performance	Risk of infection in the event of blood damage or poor administration
Substances that increase muscle mass and strength (anabolic steroids)		
Testosterone	Increases muscle development	Liver diseases and hair growth in women
Nandrolone	Increases strength, power, aggressiveness and speed	Liver problems and decreased sexual desire
Estanozonol	Testosterone derivative that promotes muscle development	Important sexual disorders

THG	Favours muscular development; synthetic drug that was designed to be undetectable	Sexual problems
Clenbuterol	Favours muscular and strength augmentation	Headache and tremors
Stimulating substances		
Cocaine	Lack of fatigue and increased aggressiveness	Addiction, anxiety, aggressiveness, tachycardia, tremors and cardiovascular accidents
Diuretic substances		
Hydrochlorothiazide	Masks the presence of other drugs by eliminating them through urine	Unusual fatigue, palpitations and yellowish eyes

Number of substances identified in each group of prohibited substances (Information provided to WADA by accredited laboratories, 2007). At this time, steroids are still the drugs that are most detected by WADA laboratories to improve athletes' performance.

Substance Group	Number*	% of all <i>Adverse Analytical Findings</i>
S1. Anabolic Agents	2,322	47.9%
S6. Stimulants	793	16.4%
S8. Cannabinoids	576	11.9%
S3. Beta-2 Agonists	399	8.2%
S5. Diuretics and Other Masking Agents	359	7.4%
S9. Glucocorticosteroids	288	5.9%
S2. Hormones and Related Substances	41	0.8%
P2. Beta-Blockers	27	0.6%
S7. Narcotics	21	0.4%
S4. Agents with Anti-Estrogenic Activity	18	0.4%
M1. Enhancement of Oxygen Transfer	3	0.1%
M2. Chemical and Physical Manipulation	3	0.1%
TOTAL	4,850	

What path does the sample take?

Samples are collected from athletes in two recipients, A and B. Sample A is used to perform the analysis and sample B is kept in reserve in case it is necessary to perform a counter-analysis. The two samples are sent hermetically closed and sealed, only bearing a numeric code, to the laboratory doing the analysis. The sample is anonymous at all times (identified only by this numeric code) and is guarded in order to guarantee security and confidentiality. All the steps followed in the extraction and analysis of the sample are written down and all instruments and procedures employed are accredited and homologated. The accreditation process for anti-doping laboratories is a double one, both by International Standardisation Organisations (ISO) and by the WADA. The reliability of the anti-doping analysis is among the most highly-controlled activities in the scientific world. There are currently 34 anti-doping laboratories that are accredited in the world (consult the Web page: <http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=333>)

Which bodies can request anti-doping controls?

There are many: the national and international federation in which the athlete competes, the National Anti-Doping Organisation (NADO) of the countries where the athlete lives or competes, the World Anti-Doping Agency, the organisers of large international competitions and the International Olympic Committee, among others.

Current legislation

The creation of the World Anti-Doping Agency in 1998 (WADA), which was initiated by Josep Antoni Samaranch when he was the president of the IOC, was the first step in the fight against doping. However, the first definitive action was the political and economic involvement of the international community and the drawing up of the World Anti-Doping Code, which started to take shape at the 2nd Worldwide Anti-Doping Conference that was held in Copenhagen in 2003. The code is a universal norm in the fight against prohibited substances that was enacted with the support of 72 countries and presently has 191 member governments. More recently, the UNESCO Convention and the 3rd Worldwide Anti-Doping Conference held in November 2007 in Madrid has driven measures forward.

In Spain, the entry into force of the Organic Law against doping and in favour of health dated February 2007, much stricter than the preceding law, defines induction and collaboration in doping cases as a crime. Likewise, Royal Decree 811/2007 of 22 June establishes the new Commission on Control and Monitoring of Health and the Fight against Doping in Sport.

The dangers of doping

Some of the most widely used substances are steroids, growth hormones and EPO. All three involve significant inherent dangers in their use that we will detail hereafter:

The most dangerous side effects of steroids that have been described in medical literature include abnormalities in renal functioning and kidney tumours, endocrine and reproductive dysfunctions, testicular atrophy, cardiac effects in the lipids and psychiatric symptoms. These consequences have been exaggerated due to the common doping practice of using 10 or more times the recommended medical dose and combining them with other drugs, such as steroids and EPO or the growth hormone.

Using growth hormone can lead to important risks, especially if we take into consideration that some reports estimate that athletes who employ growth hormones to improve performance are taking 10 times more than the therapeutic dose. Some side effects of the growth hormone are abnormal bone growth, high blood pressure, cardiovascular diseases, cardiomyopathy, glucose intolerance, polyps on the colon, decreased life expectancy and cancer.

Like steroids and growth hormones, a dose that is larger than normal is also injected when doping with EPO, which can cause increased blood viscosity, coronary thrombosis, cerebral infarction and death. It is estimated that a good number of European cyclists have died due to EPO abuse, making it one of the most dangerous doping agents.

Future challenges

Thanks to WADA initiatives, some state anti-doping agencies (for example USADA) and national research programmes have multiple lines of research focused on detecting new doping substances.

With regard to the Anti-Doping Laboratory of the Municipal Medical Research Institute (IMIM-Hospital del Mar) in Barcelona, some of the lines of research are focused on:

- **Detection of increased oxygen availability:** Erythropoietin, gene therapy, blood transfusions

Erythropoietin: Currently, work is being done on some endogenous substances that the pharmaceutical industry produces via recombination, especially 1st, 2nd and 3rd-generation erythropoietins, with the objective of characterising their differences with respect to the hormone produced endogenously.

They are also trying to develop monoclonal antibodies against N-glycolylneuraminic acid, a monosaccharide present only in recombinant material, with the objective of developing a highly-sensitive technique. Future plans are based on the development of instrumental methodologies for the detection of the presence of modifications to protein glycosylation (the addition of a carbohydrate to a molecule), which are the factors responsible for the differences between endogenous and exogenous EPOs.

Gene therapy is advancing as one of the most important therapies of the 21st century. The idea of this genetic doping technique seems relatively simple: instead of injecting a substance into the athlete's body, his muscles are enriched with the gene that produces the substance. The result is the same but detection is more complicated, since it appears as a substance generated by the body in analyses. In the world of sport, diagnostic detection of the application of gene therapy (genetic doping) could be used to prevent the bad practice of such an important medical tool. The research project is aimed at learning more about this diagnostic capability, in coordination with the main gene and image groups from the Barcelona Biomedical Research Park. There is no current proof of the utilisation of this method as a doping procedure in humans, although it is believed that it may be a reality in a very close future.

With respect to blood abuse, the objective consists of developing methods to detect abuse through blood transfusions in athletes. Two focus points will be studied: the first is based on the detection of contaminating agents present in the cavities to store blood or leukocyte concentrations; concentrations of these contaminating agents and their metabolites should be higher in the bodily fluids of individuals that undergo blood transfusions compared to subjects who do not receive transfusions. The second focus is based on the detection of aging markers in leukocytes for the storage of blood in subjects who receive transfusions.

- **Detection of growth factors:** Growth hormone, growth hormone secretagogues, chorionic gonadotropin, steroids, gene therapy and glycoconjugates.

Growth hormone (GH) is one of the most susceptible hormones due to being the object of abuse both by athletes and by the parents of children who show low idiopathic heights. Better knowledge of its detection and its structural parameters is truly useful for preventing its abuse, especially if taking into account the complexity of its structure caused by multiple isoforms (direct, joined and proteolytically derived) that are present in the human body. With respect to detection, the development of an analytical tool is very interesting to measure the ratio between the two most abundant growth hormone isoforms (20 and 22kDa). The illicit use of a drug with a single isoform would alter this ratio through a reaction mechanism and, thus, in turn, would represent an abuse indicator.

Possible abuse of GH gene therapy is also a possibility that must be prevented in the future and a project is being developed with a similar protocol to the one mentioned for erythropoietin.

Another future alternative method to produce high GH concentrations is the application of growth hormone secretagogues (analogous to ghrelin). A project is being developed to study the detection of these GH secretagogues via a single calibration protocol.

Complementary information:

<http://www.wada.org>

<http://www.imim.es/programesrecerca/neuropsicofarmacologia/grbsa.html>

http://www.imim.es/ofertadeserveis/en_laboratoriantidopatge.htm