"Biomedical Side Effects of Doping" is the summary of the scientific outcomes based on an international symposium organised by the Institute of Public Health Research at the Technische Universität München (TUM) in October 2006. The chapters of the manual take a critical look into the different doping issues, preventive actions and knowledges of the public on these topics. Furthermore, a detailed analysis is given how various doping substances can affect health of the different body systems.

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Congress Manual:

BIOMEDICAL SIDE EFFECTS OF DOPING

International Symposium October 21\textsuperscript{st}, 2006

Munich, Germany

edited by:

Hande Sarikaya
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Thorsten Schulz
Martin Schönfelder
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Project of the European Union
Preface

Addressing health effects related to doping in sports is an important priority for the European Union and its Member States. While the EC Treaty does not include a specific legal basis to fight doping in sports, in the field of public health, the Community takes action to complement Member States’ activities in reducing drugs-related health damage, including information and prevention.

In 1999, the Commission adopted a Community support plan to combat doping in sports. In parallel, we have been able to support the project on biomedical side effects of doping coordinated by the “Technische Universität” Munich from the Public Health Programme 2003-2008.

Recent international sports events were a reminder of the need to keep up the struggle against doping. Although controls, laboratory analysis and related activities have expanded, a lack of knowledge regarding the side effects of doping remains among the general public, the athletes and the sporting world. Greater knowledge of the immediate and the long-term physical and psychological effects of doping are essential among trainers and athletes, particularly young athletes, to resist the lure of doping.

Combining licit and illicit substances in doping leads to complex health effects, which are difficult to manage in particular in adolescence. Through this project financially supported by the Commission, the current level of scientific knowledge on biomedical side effects caused by doping is being coordinated.

I trust that the work of the “Technische Universität” of Munich will contribute considerably to harmonising knowledge about the biomedical side effects of doping and I congratulate the “Technische Universität” of Munich for the production of this manual.

Markos Kyprianou

European Commissioner for Health
Preface

One new doping scandal after the other is shattering the foundations of sport, for drug abuse and doping methods are not only serious dangers to the life and health of the sportspersons themselves, but are just as dangerous for sport as a whole, where the first rule should be fairness. If the public gains the impression, that manipulation has become a basic component of competitive sports, then sport’s role as a model of behaviour for the young will also be lost, resulting in the loss of the essential legitimation for state sponsorship of sport.

This goes to show that the campaign against doping is basically all about sport. Because of its deep social roots in our society, this matters a great deal! This is why the Bavarian Free State took the initiative of introducing an anti-doping law, which should improve the methods of prevention as well as the means of penalising and, as a result, should supplement the rules and regulations already available in the world of sport itself.

With the common aim of effectively fighting drug abuse, the State and sports authorities have, however, to rely entirely on highly qualified scientists, who have set themselves the same targets. This is why it is a great pleasure for me to welcome you all here to Munich, to the international symposium “Biomedical Side Effects of Doping”. In this regard, I would like to express my thanks to the TU Munich for organising this symposium, providing proof once again of why it belongs to the league of top universities.

I would like to wish all participants deep, lively discussions in their fields and rewarding insights, as well as good, lasting memories of Munich, of the city and its sights and of Bavarian hospitality.

Siegfried Schneider
Bavarian Minister of Culture
Preamble

Sport connects people, promotes health as well as personality development and in the meanwhile it is a substantial component of leisure activities worldwide. The practice and pursuit of a fair and drug-free sport are matters of public interest. More particularly, it reflects the common interest of athletes, coaches, sport facilities and governments all over the world.

The public community is hardly informed about the issue of drug abuse in sports and the health hazards which may occur. In some European countries the issue of doping is completely negated. Therefore, the aim of the present project, financially supported by the European Commission in the field of public health, is to harmonise the scientific state of knowledge about the biomedical side effects of drug abuse in sports throughout Europe and to make the information available for the general public of all European countries.

During an international symposium with the topic “Biomedical Side Effects of Doping” situated in Munich in October 2006 the actual state of knowledge concerning doping related issues and health hazards was presented to the public by well known international experts. Reacting to the increasing incidence of doping violations in sport that has been evident in recent years, the international community has established some new prevention strategies and programs that grab this problem at grass-roots level. Doping related problems as well as possible prevention strategies were discussed with scientists, coaches, physicians, politicians and further interested guests from 22 nations.

As one major outcome the scientific results presented during this symposium are summarized within the present manual accompanied by further important doping related topics. The chapters take a critical look into the different doping issues, preventive actions and knowledges of the public. Furthermore, a detailed analysis is given how various doping substances can affect health of the different body systems.

Further part of the whole European project will be the development of an interactive internet platform containing versatile information concerning doping related issues including teaching material in several European languages to improve doping prevention on an international European level.

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Contents

1 INTERNATIONAL CONVENTION AGAINST DOPING IN SPORT .................................. 1
   Paul Marriott-Lloyd

2 THE DOPING ISSUE .......................................................................................... 16
   Barrie Houlihan

3 HEALTH SIDE EFFECTS OF DOPING SUBSTANCES
   3.1 Supporting Apparatus and Musculoskeletal System ......................... 34
       Hande Sarikaya, Horst Michna
   3.2 Cardiovascular System ....................................................................... 45
       Asterios Deligiannis, Evangelia Kouidi
   3.3 Respiratory System ............................................................................. 55
       Katerina N. Georgieva
   3.4 Gastrointestinal Tract and Liver ......................................................... 66
       Carl Müller-Platz, Tsuyuki Nishino, Hande Sarikaya
   3.5 Reproductive and Endocrine System ................................................. 89
       Katerina N. Georgieva
   3.6 Renal Disorders and Electrolyte Metabolism .................................. 112
       Nikolaos Koutlianos, Evangelia Kouidi
   3.7 Immune System and Skin:  
       The Importance of Studying this Problem ................................... 119
       Eduardo Ortega, Mª Dolores Hinchado, Esther Giraldo
   3.8 Psychological Effects and Addiction including CNS .................... 135
       Ryszard Grucza
4 Actual Topics of Interest
4.1 Nutritional Supplements – Creatine................................. 154
   Martin Schönfelder
4.2 Gene Doping............................................................................. 186
   Thorsten Schulz
4.3 Narcotics................................................................................... 209
   Ryszard Grucza, Andrzej Pokrywka, Dorota Kwiatkowska
4.4 Cannabinoids ........................................................................... 223
   Peter Van Eenoo, Frans T. Delbeke

5 The Knowledge of Different Target Groups in the Fight Against Doping
........................................................................................................ 231
   Christiane Peters

6 Doping in Handicapped Sport............................................................... 245
   Christiane Peters

7 Prevention Strategies
7.1 Overview About the Actual Status Quo in Europe............... 250
   Hande Sarikaya, Jezabel Ohanian, Asterios Deligiannis, Katerina N. Georgieva,
   Esther Giraldo, Ryszard Grucza, Mª Dolores Hinchado, Nikolaos Koutlianos,
   Dorota Kwiatkowska, Eduardo Ortega, Christiane Peters
7.2 Drug Prevention and Health Promotion for High School Athletes:
   A Summary of the ATLAS and ATHENA Programs............. 262
   Melissa B. Durham, Linn Goldberg

8 Poster Abstracts................................................................................. 278

9 Symposium Program........................................................................... 306
1 INTERNATIONAL CONVENTION AGAINST DOPING IN SPORT

Paul Marriott-Lloyd

On 1 February 2007, the International Convention against Doping in Sport entered into force. This landmark occasion signified the most successful international convention in the history of the United Nations Educational, Scientific and Cultural Organization (UNESCO) in terms of the speed of its development and entry into force. Important as this achievement might be, the enactment of the Convention is of greater significance to the future of sport. Never before have global anti-doping efforts been stronger and more focused on providing an honest and equitable playing environment for athletes. The Convention provides the hitherto absent legal framework with which all governments can address the growing prevalence and increasingly insidious use of performance-enhancing substances and methods in sport. This is significant because there are specific areas where only governments can progress anti-doping efforts. It is no coincidence that all of the major doping scandals, for example Festina in 1998, BALCO in 2003 or the ongoing Operation Puerto, were uncovered by government agencies. Further action is required to target athlete support personnel, to curtail trafficking and to regulate dietary or nutritional supplements which all fall under the aegis of governments. The Convention also helps ensure coordination of testing and the development of education, training and research programmes. This chapter discusses the development of the Convention, outlines the obligations it imposes on governments and examines why doping in sport has become relevant to the international system.

A Rationale for Action

It was natural for UNESCO, an organisation that stands on principles of equality and justice, to have facilitated the development of the Convention, particularly given its education and sport mandate. UNESCO was deeply concerned about the erosion of ethics and the gross inequity created by the use of performance-enhancing substances and methods. The Convention provides the hitherto absent legal framework with which all governments can address the growing prevalence and increasingly insidious use of performance-enhancing substances and methods in sport. This is significant because there are specific areas where only governments can progress anti-doping efforts. It is no coincidence that all of the major doping scandals, for example Festina in 1998, BALCO in 2003 or the ongoing Operation Puerto, were uncovered by government agencies. Further action is required to target athlete support personnel, to curtail trafficking and to regulate dietary or nutritional supplements which all fall under the aegis of governments. The Convention also helps ensure coordination of testing and the development of education, training and research programmes. This chapter discusses the development of the Convention, outlines the obligations it imposes on governments and examines why doping in sport has become relevant to the international system.

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enhancing drugs by athletes. Doping poses one of the biggest threats to sport today. It harms athletes, destroys fair play and equitable competition and does irreparable damage to the credibility of sport. However, the impact of doping goes far beyond the athletes concerned or sport itself. It is a problem that affects all of society by undermining the intrinsic value of sport.

Sport can be a powerful vehicle for peace by forging social ties and networks, mutual respect and understanding between peoples. Sport contributes to development, drawing individuals together, providing facilities and access to community services. It is also an important learning tool for young people. During the playing of games and sport children learn about fair play, teamwork and cooperation. These lessons help to shape attitudes and values, and provide models of good conduct that last a lifetime. “That is why the United Nations is turning more and more often to the world of sport for help in our work for peace and our efforts to achieve the Millennium Development Goals.” [1] It also explains why the unanimous adoption of the Convention by the UNESCO General Conference in 2005 was considered one of the triumphs of the International Year for Sport and Physical Education.

Doping seriously threatens the ethics and values upon which sport is based. These principles are embodied in the 1978 International Charter of Physical Education, which was amended in 1991 to make reference to the doping problem:

“No effort must be spared to highlight the harmful affects of doping, which is both injurious to health and contrary to the sporting ethic, or to protect the physical and mental health of athletes, the virtues of fair play and competition, the integrity of the sporting community and the rights of people participating in it at any level whatsoever.” [2]

Anti-doping programmes, therefore, seek to preserve the essence of sport characterised by values such as honesty, fairness, respect, courage, commitment and solidarity.

The potential for athletes to act as role models should not be underestimated. Sportspersons are held in high regard in modern society. Young people in particular are fascinated by athletes and often seek to emulate their deeds. Perhaps this helps to explain why 6.1 percent of American teenagers have taken steroids without a prescription one or more times during their lifetime [3]. Research in other countries also indicates growing use of doping substances, perhaps for image enhancing purposes, across society but particularly among the young [4].
The harm caused by the use of performance-enhancing drugs and methods is a compelling rationale for action. The contributors to this publication provide scientific evidence about the biomedical side effects of doping on the cardiovascular, musculoskeletal, reproductive, endocrine, immune and respiratory systems. Examination of the impacts on the gastrointestinal tract, liver, kidneys and electrolyte metabolism as well as psychological effects are also presented. This research is vital because anti-doping efforts must be underpinned by a solid evidence base. One of the three criteria for the inclusion of a substance or method on the Prohibited List maintained by the World Anti-Doping Agency (WADA) is “medical or other scientific evidence, pharmacological effect, or experience that the use of the substance or method represents an actual or potential health risk to the athlete.” [5]

Competitiveness and the fixation on records in elite sport incite doping. Drug use may help to deliver results as a complement to dedicated training programmes and natural sporting prowess. For an athlete attuned to continual improvement (stronger, higher, faster), performance-enhancing drugs allow for an extension of the physical strength ceiling and greater adaptation [6]. The use of ergogenic agents can therefore mean the difference between a first place finish, where lucrative prizes and endorsements accrue to the winners, or otherwise. While some athletes are willing to take considerable risks to achieve sporting fame and fortune, this practice constrains the choice of others to remain drug free. Use by one athlete often forces others to follow in order to remain competitive, resulting in a form of sporting brinksmanship. The impact of doping is therefore not only limited to the athletes that consume the substances.

B International Response

In developing the Convention, UNESCO responded to calls from the international community. Concern was expressed at the dearth of ethical values in sport, manifested by doping, by the Third International Conference of Ministers and Senior Officials Responsible for Physical Education and Sport (MINEPS III) in 1999. Countries were urged to take concerted action. Sports Ministers also endorsed the outcomes of the World Conference on Doping in Sport convened by the International Olympic Committee, which led to the establishment of WADA. This unique organisation, a partnership between governments and the sport movement which enshrines cooperation and collaboration, is charged with the elimination of doping in sport.

Doping was a key item during the UNESCO-initiated Round Table of Ministers and Senior Officials Responsible for Physical Education and Sport in 2003. The
final communiqué, issued on behalf of 103 Member States and 20 intergovernmental and non-governmental organisations, highlighted the danger posed by doping in sport, not only as a breach of sporting ethics but also as a danger to public health. The participants committed to the preparation of an international convention focused on education, information, research, controls and sanctions before the 2004 Summer Olympic Games and no later than the 2006 Winter Olympic Games.

A critical juncture was the adoption of the World Anti-Doping Code (the Code) on 5 March 2003 during the 2nd World Conference on Doping in Sport. This document provides a comprehensive framework to protect the fundamental right of athletes to participate in doping-free sport and to ensure harmonised, coordinated and effective anti-doping programmes at the international and national levels with regard to the detection, deterrence and prevention of doping [5]. While a large number of sporting organisations signed the Code and ensure its global application through a series of cascading relationships, it is not legally binding for governments. In fact, governments cannot be direct parties to the Code because of its legal status and that of WADA under whose authority it was elaborated. The Code is a non-governmental document that operates in the realm of private or contractual law and WADA, despite equal governmental involvement in its funding and management, was established as a private foundation. Therefore, governments could only give a moral commitment to the Code by signing the Copenhagen Declaration on Anti-Doping and Sport. Only an international convention can create binding obligations on governments.

These developments culminated in the decision by the UNESCO General Conference in 2003 to develop an international convention to remove doping from sport. The Convention was developed after extensive drafting and consultation meetings involving representatives from over 95 countries. It was the product of three meetings of an experts group and three intergovernmental meetings between 2004 and 2005. Further, the Fourth International Conference of Ministers and Senior Officials Responsible for Physical Education and Sport (MINEPS IV) considered the draft Convention and helped to resolve a number of outstanding issues. The final Convention, adopted on 19 October 2005, met the objectives of providing an internationally recognised legal framework to: (1) ensure that governments take actions against doping in sport that are complementary to those already being taken by the sporting movement, including anti-doping activities at the national level, international cooperation, education and training, and research; (2) provide support for the Code and for other international standards developed by WADA, recognising the importance of these documents in harmonising policy and practice worldwide.
The Convention was also drafted to keep pace with changes in the international anti-doping environment. There is a mechanism that allows the Conference of Parties, the sovereign body of the Convention, to approve changes made to the Prohibited List and the Standards for Granting Therapeutic Use Exemptions (TUE). Both documents are integral parts of the Convention because they are fundamental to international harmonisation. It is essential to establish a single Prohibited List based on the latest scientific knowledge so that athletes and athlete support personnel are fully aware of the substances or methods prohibited in-competition, out-of-competition and by particular sports. Universal acceptance of therapeutic use exemptions is important so that athletes may be prescribed medicines contained on the Prohibited List for legitimate medical purposes. Any changes made by WADA to these two standards can be rapidly incorporated into Convention following approval by the Conference of Parties either in session or via written procedure. In this way the Convention can be seen as a living document.

C Complying with the Convention

The purpose of the Convention is to promote the prevention of and the fight against doping in sport, with a view to its elimination. It has been designed to coordinate and compel government action in specific areas beyond the domain of the sports movement. Where the Code only applies to members of sports
organisations, the reach of governments allows a systemic approach to anti-doping encompassing a broad range of actors.

The Convention outlines clear obligations required of governments. States Parties undertake to: (1) adopt appropriate measures at the national and international level consistent with the principles of the Code; (2) encourage all forms of international cooperation aimed at protecting athletes and ethics in sport and sharing the results of research; (3) foster international cooperation between States Parties and with WADA in particular. However, the Convention is a permissive document and it provides flexibility in the approach governments can take to implementation, either by way of legislation, regulation, policies or administrative practices.

**Availability of performance-enhancing drugs**

The first problem the Convention seeks to address is the availability of performance-enhancing drugs. Under Article 8 of the Convention, governments are obliged to limit the availability of prohibited substances and methods in order to restrict their use in sport. These include measures against production, movement, importation, distribution, sale and trafficking. At the same time there is the need to ensure that these measures do not impede the general availability of medicines or therapeutic products for legitimate purposes or to prevent their use by athletes who obtain therapeutic use exemptions. This balance can be achieved by separating use and possession from issues of supply.

The Code, Prohibited List and TUE Standard provide the framework to restrict the use of performance-enhancing substances and methods in a sporting context. It is an anti-doping rule violation to use, attempt to use, possess, administer or traffic substances or methods contained on the Prohibited List without a TUE. Governments are encouraged to reinforce these provisions. One such means is medicines-control legislation, which makes listed drugs prescription-only medicines to be dispensed by licensed medical practitioners for therapeutic purposes. Within this clinical setting athletes can also document legitimate medical conditions as the first step towards obtaining a TUE.

The issues of supply, trafficking (if a specific legal prohibition exists) and manufacture are more complicated and pressing. It makes a mockery of anti-doping efforts when an athlete incurs a two-year to lifetime ban, while those manufacturing and supplying the very same substances escape serious punishment. The BALCO and Operation Puerto investigations confirmed what
had long been suspected - there are business networks operating on the margins of the law with the express purpose of furnishing athletes with performance-enhancing substances and methods. Moreover, these businesses are well frequented by athletes and derive substantial financial gains from this trade.

There is an expectation that governments will introduce concrete measures under the Convention to curtail the supply of performance-enhancing substances and methods. Tangible actions include the imposition of border controls and criminal penalties and for this matter to be afforded priority by enforcement agencies. Italy, France and more recently Spain, within their anti-doping legislation, have created criminal offences for the unauthorised or illicit supply of performance-enhancing drugs or methods. The Australian Customs Service has successfully instituted border controls to stop trafficking, most notably prior to the 1998 FINA World Swimming Championships. Finally, the United States, having amended the penalties for offences involving anabolic steroids under the Anabolic Steroid Control Act in 2006, recently arrested a number of individuals involved in a steroid and prescription drug manufacturing operation. Further arrests and prosecutions are expected from increased government involvement in anti-doping.

**Athlete support personnel**

The Convention seeks to target all those who are complicit in the doping violations of athletes. Previously, it was difficult to deal with the coaches who used their privileged relationship with athletes to encourage the use of performance-enhancing drugs or methods. For example, Kelli White has spoken publicly of the influence of her coach Remi Korchemny in her decision to take a range of drugs, including modafinil and tetrahydrogestrinone supplied by BALCO [7]. This is not an isolated case. Behind every anti-doping rule violation committed by an athlete there are those who facilitated the doping. Some might play an intermediary role introducing the suppliers of ergogenic substances to athletes. Not to mention disreputable doctors that are willing to give blood transfusions or apply their knowledge of the pharmacopoeia - those who forget the Hippocratic Oath and put profit or prizes ahead of the health of the athlete. Anti-doping efforts had been constrained up until this point by the fact that these people could not be held accountable or penalised for their actions because they were not actual members of sporting organisations. This is one of the obvious limitations arising from the contractual basis on which the Code operates.
Under Article 9 of the Convention governments are obliged to adopt measures aimed at ‘athlete support personnel’. This term is broadly constructed to refer to all persons involved in sport, working with or treating athletes. It includes coaches, trainers, managers, team support staff, agents, administrators, officials, and medical or paramedical practitioners. Governments may need to extend those legislative changes outlined in the previous section to target those complicit athlete support personnel. Other approaches depend on the amount of leverage governments have over these persons, however, medical professionals present an obvious target. Their licences or practicing certificates should be revoked if they are found to be complicit in doping.

*Nutritional supplements*

Measures are required to deal with dietary or nutritional supplements (Article 10), a key area of concern for the anti-doping movement. Questionable business practices abound in this highly unregulated industry. Products often vary between batches, are mislabelled, contaminated or contain prohibited substances in a deliberate attempt to circumvent food or drug legislation. Several recent studies have shown that common supplements available in a number of countries contain banned substances, including stimulants, hormones, pro-hormones (for example, nandrolone or testosterone) and anabolic androgenic steroids. It is estimated that 10-20 percent of these products may be contaminated [8]. This situation is problematic if we take into account the high prevalence of supplement use by athletes. Putting aside questions about the safety and efficacy of these products, their use by athletes poses significant risks to their careers. Taking a tainted supplement could result in a two-year or lifetime ban. This is because anti-doping violations under the Code are based on strict liability. The mere presence of a prohibited substance in a blood or urine sample provided by an athlete constitutes an anti-doping rule violation. The manner in which the substance was ingested by the athlete, inadvertently or otherwise, might only impact on the length of the sanction imposed if no significant fault or negligence can be demonstrated.

Article 10 of the Convention attempts to deal with the problems concerning supplements. Governments are obliged to encourage producers and distributors of dietary or nutritional supplements to establish marketing best practices, including information regarding the analytic composition of their products and quality assurance. Effectively, this means self-regulation or the development of a certification scheme to improve labelling and production. It is doubtful if this alone provides sufficient certainty for athletes and the possibility of further
government intervention remains. However, some anti-doping organisations have also taken to testing to determine the constituents of supplements. They are then in a position to provide assurances or to issue warnings if the products contain banned substances. Others strongly warn athletes against the use of any supplements.

Doping control

International efforts will be at their strongest if athletes can be drug tested anywhere in the world at anytime. Under Article 11 of the Convention, State Parties shall support or provide testing programmes. All doping controls shall be consistent with the Code and include no-advance notice, out-of-competition and in-competition testing (Article 12). Further, international cooperation between anti-doping organisations, public authorities and sports organisations is encouraged. Through coordination, the costly and unnecessary duplication of doping controls, not to mention the inconvenience for athletes, can be avoided.

It is fair to say that doping controls are the most developed and well-known aspects of the world anti-doping programme. In 2005, the WADA accredited laboratories analysed 183,337 blood or urine samples of athletes, which represented an 8.4 percent increase on the previous year [9]. Having said that, there are still many countries were athletes are not tested at all. In order to expand the network of countries that undertake regular drug testing and to build capacity, WADA has developed Regional Anti-Doping Organisations (RADOs) composed of government and sport representatives. Their purpose is to establish effective anti-doping programmes among countries in a distinct geographical region through the coordination of testing as well as the training and funding of doping control officers. RADOs are also responsible for results management and appeals, as well as the dissemination of education and information materials. These regional organisations allow small or less developed countries to develop testing programmes whilst maximising economies of scale and the sharing of expertise and costs. To date, 10 RADOs have been established across 91 countries, while five others involving a further 31 countries will be launched during 2007. The result is that there should be no place to hide from the all-essential drug testing.

The emphasis placed on out-of-competition testing is important. It is often at international competitions that athletes are tested for the first time. By then it may be too late. Many of those using performance-enhancing drugs would have long since completed their cycles, ceasing their use well in advance of competition to allow these drugs and their telltale metabolites to clear their
system. As one commentator suggested, only stupid or careless athletes ever get caught during in-competition drug screens [10]. Out-of-competition testing is a more constant threat to would-be cheats and the latest talk is of ‘intelligent testing’. This refers to doping controls when the risk of doping may be increased, for example during training or immediately following an injury.

**Financial leverage**

As highlighted above, there is a clear expectation that all States Parties institute effective national testing programmes. Under the Convention, governments shall, where appropriate, provide funding to support a national testing programme across all sports or assist sports organisations and anti-doping organisations in financing doping controls. The Convention also seeks to maximise the leverage that governments have through the power of their financial contributions. This is considerable given that sport does not typically exist without some level of government funding, direct or indirect. Governments are required to withhold financial support to athletes and prevent their access to sporting facilities upon conviction of an anti-doping rule violation for the period of their ban. Clearly cheats should not prosper. Governments should also withhold financial or other support from sports organisations not in compliance with the Code. The public interest is not served by propping up those sporting organisations that do not commit to, or meet their obligations, in the fight against doping in sport.

**Education and training**

The Convention requires governments to support, devise or implement anti-doping education and training programmes (Article 19-23). Athletes are the primary audience and at a minimum, should be informed of their rights and obligations, and made aware of prohibited substances and methods, doping control procedures and relevant aspects of Code. Education on the potential risks posed by the use of nutritional supplements is specifically listed. For the sporting community, these programmes should provide accurate and up-to-date information on the ethical or health consequences of doping. Moreover, all members of sports organisations, athletes and athlete support personnel should participate in ongoing education programmes. For this latter group, the Convention also calls for the establishment of professional codes of conduct based on best practice and ethics.
Prevention will be best achieved through the education of athletes and the wider sporting community. It is also important to sensitise the general public to the harm caused by doping. What place would it have if all spectators, participants, administrators and sponsors demand doping-free sport?

While the need for anti-doping education may be self-evident, it does not attract a commensurate level of attention or resourcing as is currently allocated to intervention. An increasing number of doping controls are being undertaken across the world, but truly effective education programmes remain sparse. A step in the right direction would be to make Article 18 of the Code dealing with education to become mandatory, backed by government programmes under the Convention. However, before embarking on particular activities it is important to re-conceptualise education. It is much more than mere distribution of information resources; true education is lasting knowledge and the application of values. Education requires commitment, investment, constant reinforcement and time to take effect. While the provision of value and skill-based education programmes remains the mandate of governments, it should be informed and supported by the sports movement. A seamless application of anti-doping education from the classroom to the sports field is required.

**Research**

Finally, the promotion of research on anti-doping is another central component of the Convention (Articles 24-27). States Parties are encouraged to undertake, within their means, to encourage and promote anti-doping research. Specific areas of focus are articulated. Clearly research is needed to close the gap between those who seek to avoid detection and the methods at the disposal of the anti-doping movement. Research into prevention, behavioural and social aspects of doping and health consequences are also highlighted, as is sports science research that is consistent with the principles of the Code.

All research should conform to ethical practices and avoid the administration of performance-enhancing drugs or methods to athletes. Adequate precautions need to be taken to ensure that research results are not applied for doping purposes. It is an unfortunate fact that those who facilitate or partake in doping are well read. The latest scientific literature is scanned for any developments that might improve performance or increase the training load athletes can sustain, while the considerable evidence of harm is selectively ignored. Some athletes even appear willing to trial drugs in the very early stages of development with no thought of contraindications.
D Implementation of the Convention

As of 15 March 2007, 48 governments have become States Parties to the Convention [11]. The rapid pace at which governments have adhered to this international instrument is without precedent. Lengthy constitutional processes involving a thorough treaty examination, consultation, parliamentary or presidential approval and in some cases, enactment of legislation need to be concluded before governments can ratify, approve, accept of accede to an international convention. The fact that so many have done so, allowing the Convention to enter in force in accordance with its Article 37 only sixteen months after the negotiations concluded, demonstrates a steadfast commitment to anti-doping.

The first session of the Conference of Parties, responsible for implementation of the Convention, was held at UNESCO Headquarters in Paris from 5 to 7 February 2007. This meeting was attended by delegations representing all but four States Parties and over fifty Member States of UNESCO participated as observers. A number of administrative items were resolved, including the adoption of rules of procedure and the election of a six-person bureau which will remain in place until the next conference in 2009. The Conference also made decisions concerning the monitoring framework for the Convention, however further work is required to harmonise reporting requirements with those under the Code and the 1989 Anti-Doping Convention articulated by the Council of Europe, and to explore the possibility of establishing a joint electronic monitoring tool. Of greater significance was the unanimous approval of the 2007 Prohibited List and for Annex I of the Convention to be amended accordingly. Effectively this means that governments and sport are united in applying the same list of prohibited substances and methods, critical to international harmonisation.

The entry into force of the Convention marks the point at which UNESCO's attention will shift from normative development towards the challenges of implementation. In this regard, dedicated funding has been set aside to assist States Parties establish effective anti-doping programmes. UNESCO seeks to build capacity around the world through the application of the Fund for the Elimination of Doping in Sport established under the Convention. This Fund, made up of contributions, gifts or bequests from Member States, private or public bodies and individuals, recognises the fact that anti-doping programs across the world are at different stages of development and that the fight against doping in sport will be best served by building a global network of capable governments.
The Conference of Parties identified three areas for the investment of the Fund. The highest priority was attached to education projects focusing on youth and sports organisations. Secondly, States Parties can apply for assistance with the development of legislation, regulation, policies and administrative practices for the purposes of complying with the Convention. Thirdly, funding was earmarked for mentoring and capacity development programmes, particularly among least developed or low income States Parties. At the same time, the governments of Canada, China, Denmark, Greece, Luxembourg, Netherlands, Norway, Russian Federation, South Africa, Spain and Sweden announced substantial financial contributions which will allow the first projects to be initiated in 2007.

UNESCO’s intent in developing the Convention was much greater than simply filling a normative void; it was an opportunity to focus renewed attention on ethics, personal responsibility and integrity. This objective, combined with the organization’s mandate and considerable experience in the development and implementation of education programmes, should help to redefine anti-doping efforts. It is important to build on the momentum behind the Convention to raise public awareness and to invest in prevention through education programmes. Ultimately, one of the keys to success will be providing quality advice to young people and building resilience among the next generation of athletes by fostering strong values and promoting sport ethics.

UNESCO is currently working with WADA and a range of partners to develop a school-based education programme for young people. This follows on from a number of workshops and youth fora and the production of educational materials which introduce young people to the issue of doping in sport in a positive and empowering manner. It is important to educate young people about the harm doping does to sport as well as to the individuals concerned. That harm is not just physical or psychological, it is also ethical. If the values of fair play can be effectively instilled, it is hoped that they will have a lasting impact.

E Conclusion

The development and entry into force of the Convention is a significant step in the fight against doping in sport. It represents the first time that governments around the world have collectively decided to focus their considerable powers and resources on tackling the doping problem. The Convention was needed to complement the actions taken by the sporting movement under the Code and to address particular limitations that have impeded progress. A series of measures for governments to avert or eliminate doping in sport and to foster cooperation are outlined. Specific actions include restricting the availability of prohibited
substances and methods, targeting those that facilitate doping, funding doping controls, addressing problems associated with nutritional supplements and promoting education as the central tool in prevention. All of these provisions, and those engaged in their implementation across the globe, share a single purpose - that future generations are able to enjoy and excel in doping-free sport.

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Sweden, Thailand, Trinidad and Tobago, Tunisia, Ukraine, United Kingdom of Great Britain and Northern Ireland.

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2 THE DOPING ISSUE

Barrie Houlihan

A The Doping Issue

It is extremely difficult to establish a clear picture about the extent of doping in sport and whether current anti-doping efforts are having an impact on the prevalence of doping. In the six months between August 2006 and February 2007 the following incidents were reported in the media. In August 2006 Finnish customs authorities seized 24,800 vials of human growth hormone and 11.8 million tablets of anabolic steroids which were in two vans crossing the border into Russia. The doping agents had entered Finland from China via Denmark. In the same year a leading German cyclist was reputed to have spent €35,000 in one twelve month period on performance-enhancing drugs and a court enquiry into drug-taking within the Cofidis cycling team heard that between 2001 and 2003 €37,000 a year was spent on drugs which allegedly included anabolic steroids, hormones, amphetamines and diuretics.\(^1\) In August 2006 Christine Ohuruogo, one of Britain’s most promising runners, was suspended from competition because she missed three drug tests. In mid 2006 nine Iranian weightlifters (out of a team of eleven) tested positive for excessive levels of testosterone prior to a competition in the Dominican Republic. Finally, in early 2007 it was reported in a television documentary that 250 German athletes, including track and field athletes, cyclists and swimmers, refused about 400 unannounced drug tests and received no penalty from the national anti-doping organisation.

Large scale smuggling, continuing problems with sports such as weight-lifting and road cycling, high profile athletes violating anti-doping rules and weaknesses in the application of anti-doping procedures and penalties provide ample evidence of both the scale and the persistence of the challenge facing anti-doping authorities. However, it is easy to let reports such as these obscure the achievements of the last few years and the progress in making doping in sport increasingly difficult. Of particular significance is the development of a global anti-doping regime centred on the World Anti-Doping Agency (WADA).

A policy regime may be defined as ‘principles, norms, rules and decision-making procedures around which actor expectations converge in a given issue-area’ \([1]\). According to Krasner (1983), ‘Principles are beliefs of fact, causation, and rectitude. Norms are standards of behavior defined in terms of rights and

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\(^1\) Guardian Unlimited (http://sport.guardian.co.uk/print/0,,329620370-108653,00.html) accessed 07.11.06
obligations. Rules are specific prescriptions or proscriptions for action. Decision-making procedures are prevailing practices for making and implementing collective choice’ [1]. The main features of the more effective policy regimes are: first, significant degree of stability in the pattern of relations between core actors; second, a process by which some interests (sports organisations and governments for example) emerge as core actors and others are marginalised; and third, the fulfilment of key functions of regime maintenance, such as information exchange, policy review and the monitoring, verification and, in some regimes, the enforcement of compliance [2-5]. Prior to the establishment of WADA the global anti-doping effort was characterised by organisational fragmentation, mutual suspicion and under-resourcing. Although the International Olympic Committee (IOC) was considered to be the lead international agency on doping issues its capacity to lead effectively was hampered by its lack of a direct relationship with athletes, its lack of leverage with governments (many of whom, such as the Soviet Union, were major instigators of elite-level doping) and its unwillingness to devote adequate resources to tackling the problem. Consequently, while there was a degree of stability in relations between key policy actors the links were weak and irregular. Key policy actors such as the IOC, the major Olympic international federations (IFs), the Council of Europe and a small number of activist governments tended to operate in relative isolation. The deep suspicion and mutual distrust between the IOC and the International Federations and between the IOC and the IFs on the one hand and governments on the other tended to stymie attempts to build more cooperative working. Consequently, the IOC, many of the major IFs and most governments were content, up until the late 1980s at least, to adopt a passive or minimalist role within the nascent policy regime consequently leaving centre stage free for a relatively small group of enthusiastic, but under-resourced and politically weak, actors such as the Council of Europe and a few 'activist' governments.

The third common feature of successful regimes is that key functions of regime maintenance, such as information exchange, policy review, monitoring, verification and, in some regimes, the enforcement of compliance, are fulfilled. Within the anti-doping regime the maintenance function was poorly fulfilled. In the absence of a permanent secretariat or an agreed division of labour regime maintenance was erratic with information exchange and debate, such as it was, confined to a relatively closed groups of actors – the IOC, IFs and activist governments – which tended to take a very narrow views of their responsibilities. Some regular forums, e.g. the Council of Europe Anti-doping Convention Monitoring Group and the IOC Medical Commission did give a
degree of stability and continuity to policy discussions, but membership tended to be limited to either state or sport actors. Overall, the anti-doping regime prior to 1999 was characterised by fragmentation of effort, a general lack of momentum and a severe lack of resources.

The establishment of WADA in November 1999 did much to strengthen the organisational infrastructure of the regime. The mission of the Agency is 'to promote and co-ordinate at international level the fight against doping in sport in all its forms. The Agency's principal task will be to co-ordinate a comprehensive anti-doping programme at international level, laying down common, effective, minimum standards, compatible with those in internationally recognised quality standards for doping controls [6]. The Board of the Agency draws fifty percent of its membership from public authorities with the remainder coming from a variety of sports stakeholders including the IOC, the IFs, national Olympic committees and athletes. The Agency, headquartered in Montreal, has a significant staff complement, a relatively secure, if not overly generous, funding base, and an expanding network of working groups and standing committees. However, WADA's most significant contribution to the anti-doping regime has been the successful implementation of the World Anti-Doping Code. The draft Code emerged against a background of increasing litigiousness among athletes found guilty of doping violations with many of the challenges based either on arguments relating to the poor management of the process of sample collection and laboratory analysis, or on the lack of consistency between the rules of the sample collection agency, the domestic federation of the athlete, and the relevant international federation. Vrijman (1995), Siekmann (1999) and Siekmann & Soek (2000) [7-9] confirm that many domestic and international federations had poorly drafted, and frequently out of date, regulations covering doping. It is not only in the areas of harmonising the management of doping control processes and the treatment of positive results that the Code has had an impact it has also resolved many of the problems arising from overlapping and multiple jurisdictions.

The World Anti-Doping Code has been an extremely successful document which not only introduced a considerable degree of harmonisation of policy and practice in anti-doping but also established a framework for continuing and closer cooperation between governments and their domestic federations. The acceptance of the Code by international sports federations, for both able-bodied and disability sport, is almost universal and all 203 national Olympic committees affiliated to the IOC are signatories. In total over 570 international sports organisations have indicated their acceptance of the Code. Although the Code is the obvious symbol of the success of WADA the Agency has been active is a
broad range of other important areas including developing athlete education programmes, providing independent observers to monitor the efficacy and fairness of doping control programmes at major sports events, and commissioning research. However, although WADA’s establishment made a major change to the international anti-doping policy regime other significant contributions have been made by the Court of Arbitration for Sport (CAS), the European Union (EU) and the United Nations Educational, Scientific and Cultural Organisation (UNESCO).

The Court of Arbitration for Sport (CAS) has emerged in recent years as an increasingly important arbitration body in international sport and is intended to fulfil a crucial appeal function in relation to the operation of the World Anti-Doping Code. CAS has been formally independent of the IOC since 1994 and deals with two types of disputes – commercial and disciplinary. A substantial proportion of the disciplinary disputes is doping-related and arrives at CAS on appeal. The Code notes the exclusive right of CAS to hear appeals from international level athletes on doping issues [10]. Since 2003 CAS has proved itself to be a robust and independent organisation which has steadily won the respect of both athletes and their international federations. Not only does CAS provide relatively cheap and quick decisions but it has contributed to the establishment of an important body of case law which has increased the sensitivity of the Code to the wide variety of circumstances in which doping violations take place.

The role of CAS in a successful anti-doping regime is crucial as there has to be some concern that the athlete will always be at a disadvantage in appeals against convictions for doping violations as s/he is facing the combined might of WADA, their IF and possibly also their national anti-doping organisation. Foster (2001) expresses this concern succinctly by arguing that ‘The power relationship between a powerful global international federation, exercising a monopoly over competitive opportunities in the sport, and a single athlete is so unbalanced. Rather like the employment contract, a formal equality disguises a substantive inequality and a reciprocal form belies an asymmetrical relationship’ [11]. However, Foster’s concern is counter-balanced by a series of opinions which suggest that CAS has shown itself capable of protecting the interests of the weaker party in anti-doping appeals and delivering a fair decision. McLaren (1998) [12], for example, notes that in a number of cases ‘CAS has endeavoured to maintain a balance in the doping offences by not literally applying the strict liability concept in some cases requiring a degree of fault before upholding the imposition of a sanction’ and Nafziger (1999) notes that in reaching its decisions ‘principles of equity seem to play a role’ [13]. CAS has
also asserted its independence of both major international federations and the IOC in finding in favour of the athlete. McLaren (1998) is confident that the growing popularity of CAS as an appellate body is due to its 'jurisprudence approach' and its lack of timidity in overruling or modifying IF or IOC decisions on doping violations. However, while taking an appeal to CAS is undoubtedly cheaper than progress through domestic courts it is not cost free and may well prove prohibitively expensive for individual athletes. Burger (2000) also notes the lack of capacity within CAS to award compensation as 'the principle deficiency' [14]. Thus the athlete who successfully establishes that a sports organisation has wronged him or her in a doping case has no means through CAS of seeking compensation for their loss. These concerns notwithstanding CAS complements the work of WADA and is an important element in the global anti-doping infrastructure.

In the past a central concern regarding anti-doping activity was the tendency for initiatives to be led by sports organisations, most notably the IOC and the International Association of Athletic Federations, or clusters of governments, for example the International Anti-Doping Agreement\(^2\), but rarely jointly by both. However, not only has WADA brought together governments and international sports organisations in its Board, but it has also been instrumental in encouraging greater involvement by the European Union and UNESCO. While the European Union has no formal responsibility in relation to sport it has used its more general responsibility for public health to intervene on anti-doping issues and to support research and has sought to coordinate the work of NADOs in member states. According to Wolfgang Schaeuble, the German Interior Minister, ‘The network [of NADOs] will in particular improve information-sharing and the coordination of NADOs regarding EU-related issues. It will also make it easier to initiate and coordinate EU-wide campaigns in the field of anti-doping policy\(^3\). More significantly, the involvement of UNESCO has dramatically strengthened the international anti-doping effort.

In October 2005 UNESCO adopted unanimously the International Convention against Doping in Sport. The Convention entered into force at the beginning of February 2007 and by the end of March 2007 the Convention had been ratified by forty-nine countries, including a number of major ‘sports powers’ such as Russia, France, Japan and China. The purpose of the Convention is to ‘promote the prevention of and the fight against doping in sport’ and as such the

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\(^2\) Formerly the Memorandum of Understanding Group which comprises included Australia, Canada, New Zealand, Norway, Sweden and the United Kingdom.

Convention is intended to provide governments ‘with the means … to back the efforts of the sporting movement … [and] to give effect to the World Anti-Doping Code, creating an obligation on nations to take steps in accordance with its principles’ [15]. The Convention is designed in such a way that it can incorporate changes made to the WAD Code without the necessity for fresh ratification.

Ratification by so many countries in such a relatively short period of time is a considerable achievement and indicates a substantial level of support from governments. Clearly there are more ratifications yet to be announced due to the slower pace of the process of approval in some countries. However, at this stage there are still twelve EU members who have not yet ratified the Convention, including Belgium, Italy and Portugal and also five countries who finished in the top fifteen places on the medals table at the Athens Olympic Games who have yet to ratify, including Italy, Germany and Cuba. It should also be remembered that 186 countries signed the Copenhagen Declaration on Anti-Doping in Sport (the governments’ expression of support for the World Anti-Doping Code) which means that there are still 137 countries yet to ratify the UNESCO Convention.

The evidence of increased government support has been matched by a similar trend among the international federations for the more commercial sports. For many years golf, tennis, football and rugby were, at best, weak supporters of a robust anti-doping policy. In general, these sports tended to deny that they had a doping problem and when they introduced drug testing it was done with obvious reluctance and with a very lenient attitude towards positive test results. Due mainly to the pressure to adopt and implement the WAD Code these sports have slowly come into line with the practices of the main Olympic sports.

B Continuing Challenges and Concerns

Despite the considerable progress that has been made since 1999 substantial challenges remain if momentum in anti-doping is to be maintained. It is one of the truisms of policy implementation and of political life generally that a long term perspective, persistence and policy innovation are rare attributes among policy-makers who are under considerable pressure to deliver rapid and immediately visible results. In discussions about doping in sport one of the most dangerous, but unfortunately common assumptions, is that doping in sport can be eliminated. However, drug free sport is about as likely as crime-free society. Anti-doping policy-makers are involved not only in a long term confrontation with doping, but are, or at least should be, working towards objectives that are
specified in terms of doping reduction rather than doping elimination. With this caveat in mind it is possible to identify a number of challenges that face WADA and other anti-doping policy makers. The discussion which follows concentrates on a series of political and organisational challenges.

C Political Challenges

Governments: Active, inactive and the ineffective

Governments can be divided into two categories – the active and the ineffective. The ‘active’ category includes the Scandinavian countries, the Netherlands, France, Australia and Canada who have a relatively long history of involvement in anti-doping policy at both the domestic and international levels. The membership of this group has hardly altered since the early 1990s. More problematic is the second category – the ‘ineffective’ – a group that would include many former communist countries in central and eastern Europe where there is nominal compliance with the WAD Code but an insufficient allocation of resources to ensure effective compliance. Other countries in this category would include the United States which has made dramatic strides to improve its previously appalling record on anti-doping, but still has much to do. Although WADA has recently identified the US as an example of a country taking effective action against the manufacture and distribution of drugs it is also the country with one of the poorest records for dealing with doping in professional sports.

Substantial doubts still surround certain sports in China especially (women’s) swimming and middle and long distance running. While China has done much to establish an anti-doping capacity it has been accused by Australian and American swimming federations of not presenting its strongest teams in international competition fuelling the suspicion that it is keeping its strongest swimmers secure against out-of-competition testing in the period before the Beijing Olympic Games. Moreover, Zhou Ming, former head coach who was banned for eight years in 1998 for involvement in doping is now back coaching. However, the fact that China won no gold medals at the Sydney Olympic Games and only one gold medal at Athens might indicate a more effective approach to combating doping in swimming. More ambiguous evidence comes from the recent raid by Chinese anti-doping officials on an athletics school in Anshan Province where 141 bottles of steroids were found in a refrigerator in the head teacher’s office. The fact that the raid took place is an indication of effective policing of the problem but the lack of any action to date against the staff at the school is a cause for concern. In a generally positive assessment of
the progress that China had made in improving its anti-doping efforts Dick Pound nevertheless drew attention to the fact that China’s 7000 tests each year compared poorly with the 8000 undertaken by Australia with its much smaller population.

In India, a country with clear Olympic ambitions, the anti-doping system is, at best, basic. India has experienced a number of positive drug tests among its elite athletes, but it has yet to establish an effective national anti-doping organisation and there is very little evidence of serious consideration of the issue of doping within the Indian Olympic Association (IOA) and the major Olympic federations. While the IOA does conduct in-competition testing there is no evidence of a capacity to conduct, the far more important, out-of-competition testing. Nor is there evidence of a capacity to maintain a database of athletes' whereabouts which is a requirement of the WAD Code. India’s record on the implementation of the World Anti-Doping Code is, to date at least, extremely poor. Even Germany, which for many years has been seen as an ‘activist’ country with a strong record on doping, was embarrassed by the disclosure that over 200 athletes had refused unannounced tests without any apparent sanction. Of 4418 planned tests there were 385 ‘no-shows' involving 201 athletes indicating that a number of athletes had refused tests more than once. Although the national anti-doping organisation was aware of the missed tests it did not pass the information on to the respective domestic sports federations.

*International federations: The reluctant few*

While formal acceptance of the WAD Code was unproblematic for most Olympic and non-Olympic International Federations some, mainly the more commercial, have experienced serious problems demonstrating compliance. Cycling provides the clearest example of an international federation struggling to come to terms with doping. The UCI is an interesting federation as it has been involved in anti-doping policy efforts since the 1960s yet, in the words of Dick Pound, WADA Chairman, ‘Whatever has been done to date has been sadly lacking’ (quoted in Cycling News, 14th August 2006). Pound’s view is confirmed by the fact that the winner of the 2006 Tour de France and the riders who came second, third and fourth in the 2005 Tour have all been accused of doping violations. Furthermore, the investigation of doping initiated by the Spanish police, Operation Puerto, provided evidence that blood-boosting drugs with a value of over £1m had been sold in Spain and south-west France each year since 2002.
Professional tennis has long remained aloof from global anti-doping debates, partly because of the weakness of the International Tennis Federation in relation to the Association of Tennis Professionals and the Women’s Tennis Association which effectively manage most of the major tour events. It was only in late 2006 that the ITF finally reached agreement with the ATP and WTA to coordinate anti-doping testing on their behalf. Cricket has also struggled to cope with the positive test results for two Pakistani cricketers, Shoaib Akhtar and Mohammed Asif. The decision by the Pakistan Cricket Board (PCB) to ban the players for two years and one year respectively was overturned by a PCB appeal panel much to the annoyance of the International Cricket Council (the sport’s international federation) and of WADA which is to challenge the decision at the Court of Arbitration for Sport.

Other highly commercialised sports like golf are also proving to be extremely slow to embrace the requirements of the WAD Code despite the fact that in France, where testing has been in operation since 2001, 13% of elite golfers produced positive test results for drugs including cocaine, and sambutamol. In Britain, however, the domestic governing body, the Royal and Ancient Golf Club, has published an anti-doping policy, but has declared it to be only ‘advisory’. In the United States the US Golf Association has the following memorably insouciant statement ‘The Committee may require in the Conditions of Competition that players comply with an anti-doping policy’ while the US Professional Golfers’ Association still maintains that there is no drug problem in golf. Finally, football spent two years from 2004 attempting to be selective about the parts of the WAD Code that it would accept. Despite a ruling from the Court of Arbitration for Sport in April 2006 that FIFA was not compliant on eight points (including the Federation’s unwillingness to accept the automatic imposition of a two year suspension for a serious doping offence) FIFA remains, at best, a reluctant signatory to the Code. The commitment of these federations must remain open to question and await more comprehensive evidence of sustained compliance.

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D Organisational and Management Challenges

Whereabouts information and missed tests

When the British runner, Christine Ohuruogo, missed three unannounced tests and was subsequently suspended from competition it was also revealed that an additional 70 track and field athletes had also missed one or two tests. At present all athletes have to notify their federation of their whereabouts so that unannounced tests can be conducted. Unfortunately, there seems to be little consistency between national anti-doping organisations regarding what whereabouts information is required, how that information is collected and stored, and what are the consequences for a failure to be available for a test on three occasions. The consequence of the lack of uniformity is considerable frustration among athletes. In the revisions to the WAD Code currently under discussion it is proposed to give much clearer guidance to national anti-doping organisations. In the draft of the new Code athletes will have to provide details of their whereabouts every quarter and identify an hour in every day of the week when they will be available. More importantly the range of penalties available has been narrowed from three months to two years to between twelve months to two years.

Penalties for doping violations

The Code requires a two year suspensions for a first violation followed by a life ban for a second violation. While allowing an athlete a second chance to compete without drugs is widely accepted the significance of the two year ban needs to be seen in relation to the competition structure and career 'life-expectancy' within particular sports. In some gymnastic events, for example, the length of time an athlete could normally expect to remain competing at the highest level is far shorter than that for a rower or middle-distance runner. Equally significantly there may only be one competition for the gymnast, usually the Olympic Games, which offers global media exposure and prestige. There might also be a lack of other means of indicating relative ability, for example the opportunity to set world, continental or national records. For the runner the IAAF World Championships have a status close to that of the Olympic Games and even for athletes who under-perform at both the Olympics and the World Championships there is always the possibility of setting a new record at other IAAF recognised events.

It is, at the very least, debatable whether the gymnast who, due to the imposition of a two year ban, misses possibly his/her only chance to compete in
the Olympic Games is being treated in an equitable fashion when compared to the 5000m runner who has a far greater likelihood of competing in a future Olympic Games as well as having the possibility of a high media profile world championships or securing his/her place in sporting history through record-setting. While a standard period of ineligibility might be administratively convenient it is inequitable and can be justified, if at all, only as an interim arrangement until such time as a sanction tariff can be introduced which is more sensitive to the characteristics of the athlete's sport and working conditions. However, there seems to be no move to introduce variable or sports-specific penalties as current debates on revisions to the Code, led by the IAAF and the IOC, are focused on increasing the penalty for a first offence to a minimum of four years and a life ban from Olympic competition.

The location of NADOs

According to WADA, best practice in anti-doping requires that not only should each country establish a national anti-doping organisation (NADO) but that ‘the NADO should be independent in decisions and actions from the sports organisations. The principle of independence from elite athlete development underpins anti-doping programs world-wide, and ensures the integrity of anti-doping work’ (WADA, 2004, Introduction). The justification for this recommendation was: first, that grant giving (a supportive function) and anti-doping (an adversarial function) were incompatible and created the potential for unethical behaviour; second, that co-location often lacked transparency and accountability; and third, that leading countries in anti-doping, such as Canada, Australia and the United States, had independent NADOs.

The recommendation for an independent NADO presented a number of countries with a dilemma due to the frequency with which doping control and the talent identification and development process were the responsibility of the same organisation – usually either a government agency (as in Canada, Australia and the UK) or the national sports confederation (as in Sweden and Norway). The response of many countries was to establish a new and independent organisation to oversee anti-doping activity.

While a new and independent NADO may be a requirement if the previous system was tainted by scandal or inefficiency there are strong arguments for maintaining an organisational link between elite development and anti-doping. First, the concept of independence is dubious in relation to NADOs. In examining the concept of organisational independence it is possible to identify four central dimensions: legal, financial, administrative and political. Given that
in many countries the legislature is dominated by the executive, legal independence is always qualified and contingent and rarely provides an effective barrier to ministerial interference. The potential for funding arrangements, the second dimension, to confer independence is similarly qualified. While it is possible for NADOs to generate some income through the sale of drug testing services to commercial sports, most of their work relies on public subsidy as ‘public interest’ is the primary justification for drug testing. The third dimension, administrative independence, suggests not only separate central services (personnel, financial, IT etc) but also a geographically separate location intended to segregate personnel. The final dimension, political independence, is the most important dimension as financial, administrative and even legal independence can be easily undermined or circumvented if there is no commitment to political independence. However, it is by far the most difficult dimension to specify. One formulation of political independence implies the acceptance of a set of values according to which intervention is normatively unacceptable. An additional/alternative view of political independence is one which requires a degree of transparency regarding NADO operations such that any undue political influence would be readily apparent. A third possibility is that the NADO is ‘patrolled’ by a cluster of stakeholder interest groups, for example for athletes, national federations and event organisers who would counter-balance not only the political influence of the government, but also the influence of each other.

The problems with an independent NADO include: the potential isolation of NADO staff from information about developments in elite training practices; the exclusion of NADO staff from policy discussions in WADA, Council of Europe and other government-based international organisations; uncertainty about the role and status of the organisation in the eyes of athletes; and the risk that the NADO develops, over time, its own norms and values which deviate from those in the broader international anti-doping regime. There are also strong arguments for locating the NADO within government which include: first, that the government grant giving (and withholding) powers in relation to elite sport reinforce the work of the NADO; second, that where independent NADOs have been established it has usually been as a result of a crisis prompted by scandal (Australia and Canada), anti-doping policy failure (USA), or previous location within the national sports confederation (Norway); third, that the cost of running an independent NADO would add between 10-15% to the cost of anti-doping activity (Houlihan & Preece 2007). Rather than focus on the dubious concept of independence WADA should ensure that NADOs are located within a clear framework of accountability and operates in a transparent manner.
Policy instruments and focus

Understandably the predominant focus of anti-doping policy since the establishment of WADA has been on the athlete and on detection, the management of doping violations and the education of the athlete. There is an increasing need to expand the scope of anti-doping activity to encompass not only the athlete’s entourage but only the rapidly growing industry that manufactures and supplies drugs to athletes. As regards the athlete’s entourage there has been an increasing concern to impose penalties on those coaches, doctors and others who contribute to and support an athlete’s drug use. However, while there has been a steady increase in the number of coaches suspended from involvement in sport the process by which a member of an athlete’s entourage can be excluded from sport is more complex and potentially expensive as guilt cannot be simply determined on the basis of strict liability and necessitates a more traditional adversarial or investigative process. However, the significance of some coaches and trainers in encouraging the use of drugs requires that anti-doping activity adapt and continues to extend sanctions beyond the athlete.

The BALCO affair in the United States provided ample evidence of the extent to which the manufacture and supply of drugs to athletes has become a major industry estimated by Donati (2007) to be providing performance enhancing drugs to an estimated 31m users world-wide [16]. While the WAD Code already allows for the punishment of those who supply drugs to athletes the punishments are confined to involvement in sport. However, the ability of NADOs to prosecute successfully drug suppliers requires close cooperation with law enforcement agencies and assumes that NADOs have resources to collect evidence to allow successful prosecution. At present there are discussions which would allow a reduction in the penalty imposed on athletes if they provided evidence leading to the prosecution of suppliers. Consideration is also being given to changes in the Code to make it an offence to fail to cooperate with an investigation and to make it an offence to lie to an investigator [17]. Australia is one of the few countries that has adopted a more aggressive approach to pursuing suppliers and reports that around 25% of its recent doping violations were uncovered due to Australian Sport Anti-Doping Agency’s new investigative powers. However, while there are clear advantages to a more robust investigative role for NADOs there are substantial cost implications and the most promising amendment to the Code might be to put give the athlete strong incentives (such as reduced suspensions) to reveal information about their suppliers and about other drug users.
Monitoring compliance with the WAD Code

The gap between formal acceptance of the WAD Code and compliance can often be substantial. Consequently, the procedures identified to monitor compliance are crucial for establishing and maintaining confidence in the anti-doping effort. However, monitoring compliance is resource intensive, particularly when dealing with a complex document such as the Code. WADA’s compliance procedures are weak as they rely too heavily on self-reporting by individual countries. At present signatories report in alternate years on their compliance by means of the completion of an on-line structured questionnaire. Apart from the general weaknesses of structured questionnaires many of the questions allow too much scope for subjective interpretation. For example one question asks, ‘Do you apply the currently enforced WADA prohibited list?’. Respondents choose between: ‘Yes, without any changes’; ‘Yes, without any substantive changes’; ‘Yes, but with a few significant changes’; ‘No’; and ‘Do not know’. How the respondent decides whether changes are ‘substantive’ or ‘significant’ is unclear. Without doubt the reliance on self-reporting is a consequence of the cost of alternatives, but it would certainly be preferable if WADA were to augment self-reporting by occasional external inspections as is the practice adopted by the Council of Europe in monitoring compliance with its own Anti-Doping Convention.

American professional sports

It is tempting to ignore the four major American sports of American football, baseball, ice hockey and basketball, on the grounds that the very few other countries play the first two and neither is an Olympic sport and also to ignore the last two on the grounds that it is only in the US that these sports are so intensely commercial. However, to allow them to assume exceptional status would be a serious mistake as these sports are in the vanguard of the steadily accelerating commercialisation and commodification sport and their intransigence on doping control has set an example which golf, football and tennis have all sought to emulate. To its credit WADA has kept the spotlight on these sports and has aided the efforts of US Congress members to try to force them into line with the WAD Code.

The National Hockey League for example introduced testing in 2006 and conducted 1406 tests. However, the programme lacks transparency as it is not clear who is administering the tests, under what circumstances, to which players and at what times. More importantly it is not clear whether the programme tests for the full range of banned substances on the WADA list. In
mid 2006 the NHL announced that none of the 1406 tests had been positive prompting Bill Daly, deputy commissioner, to claim, rather disingenuously, that the results showed that ‘doping is not a problem in our sport’. The National Basketball Association has had a drug policy since 1984 (to test for cocaine and heroin), but only started to test for steroids and marijuana in 1999. Only three players have been suspended for doping offences since 1999. Not only is there a similar lack of transparency within basketball as in ice hockey, but its sanctions are weak (suspension for 10 games for a first offence by comparison to WADA’s two year suspension). Major League Baseball has long been reluctant to address the issue of doping. Like American Football many baseball team owners see drug use as having boosted spectator numbers due to the greater prevalence of offensive play – more attacking play in football and more home runs in baseball. Not surprisingly positive tests results, when they are made public, result in negligible sanctions. For example Shawne Merriman, the San Diego Chargers linebacker, who breached the NFL’s steroid policy, was given a four game suspension.

E Conclusion

As this review has illustrated that the short period since 2003 has witnessed considerable strengthening of the global effort to combat doping in sport. The infrastructure of the anti-doping policy regime is firmly in place with WADA, CAS and UNESCO at its heart and with the WAD Code a key policy instrument. The review of the Code that began in 2006 provides an insight into two important aspects of the work of WADA: first, the modest scale of proposals for amendment is indicative of the extent to which the Code has generated support across a range of countries and sports and among athletes as well as sports organisations; and second, the commitment to regular reviews of the Code indicate the extent to which it is seen as a living document seeking to adapt itself to changes in what is clearly a dynamic policy environment.

However, the review also makes clear that many substantial challenges remain and that combating doping in sport is going to be a permanent feature of sport at the highest levels. Perhaps the most important challenge facing the policy regime is building the capacity among poorer and less politically committed countries. Government commitment is the essential first step in ensuring commitment by national federations. Nowhere is this better illustrated than in

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5 News story from the Globe and Mail: www.theglobeandmail.com/servlet/story/RTGAM.20060613.wpound13/
the United States where the absence of doping from the mainstream political agenda allowed a deep cynicism and corruption to establish itself across a broad range of Olympic and commercial sports. The change of priorities in the late 1990s, signalled by General Barry McCaffrey’s appointment as Director of the Office for National Drug Control Policy under Bill Clinton and his strong lead on doping in sport, has had a dramatic impact on one of the most corrupt sports systems outside the former communist bloc countries. Unfortunately, as was made clear in the earlier discussion, much still remains to be done to bring the United States into line with the leading countries on anti-doping policy. Moreover, there is a long list of countries which still deserve scepticism towards their anti-doping activities including most of the countries of the European former communist bloc, a large number of countries in the Middle East, India and China.

The fundamental challenge facing all policy actors concerned with anti-doping policy is to be able to maintain, over the next twenty to thirty years, political commitment and the legislative, financial and administrative resources that follow from that political commitment. However, the achievements of the last five years are considerable and provide a strong foundation for establishing a sustained and well resourced commitment to combating doping in sport over the medium to long term.

F References

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Speculations shadow peak performances in sport since it is known that there exist an unlimited number of substances which enhance physical performance: Did this bodybuilder win that contest without abusing androgenic anabolic substances? Did Tour de France Champions abuse EPO? Are all present world records in sport achieved illegally? What are the consequences of using forbidden substances in suprapharmacological doses and what side effects will cause modern gene doping? Finally, a lot of high level sport athletes suffer or even die from biomedical side effects of doping during or after their career.

One major problem is that at the height of steroid development in the 1960`s and 70`s pharmaceutical companies researched dozens of potential drugs and picked the one that worked best in trials. Therefore, there are thousands of abandoned steroid projects that could be easily converted to the next Nandrolone, Desoxymethyltestosterone or Tetrahydrogestrinone concerning androgenic anabolic steroids. Similar undesirable progression may happen in all substance classes and methods used illegally in high level sports to say nothing of upcoming gene doping.

Doping issues have also become a social problem just as illegal narcotics already are. All-purpose drugs for all imaginable use are available on the streets while most peoples/customers don't know if they are harmful to health or illegal.

The conclusion is that it is most important to highlight the perilous potential of such abused substances not only among high level athletes but also in public especially if used for performance enhancement typically in suprapharmacological doses.
3.1 SUPPORTING APPARATUS AND MUSCULOSKELETAL SYSTEM

Hande Sarikaya, Horst Michna

A Introduction

Athletes may be tempted to use a range of different hormones for a variety of reasons. But as sports does not automatically include a course on pharmacology, most athletes have only a poor knowledge regarding these substances especially concerning their adverse health effects. The application of additional hormones or drugs to a healthy person modifies the normal hormonal balance of the body, which attempts to redress this balance. The warnings concerning these impacts and potential dangers are often neglected. The athletes self-administering ergogenic aids to increase their competitive edge continue to be a problem. But the gap of knowledge applies not solely to professional athletes. Recreational sportsmen and coaches are not proficient in the field of health side effects of ergogenic aids, too. It is thus essential that athletes, both recreationally and professionals, and coaches etc., learn and understand that the careless abuse of illicit drugs has severe consequences on health. In this context, this review focuses on the adverse health effects and the problems connected with the use of illicit drugs on the supporting apparatus and musculoskeletal system.

The human musculoskeletal system consists of the skeleton, made by bones attached to other bones with joints, and the skeletal muscle attached to the skeleton by tendons. Understanding the structures and functions of human muscles has long occupied scientists. As muscles do not replicate throughout life, the human body is endowed with the capacities to induce muscle repair and to prevent cell death. Whether the individual is young or old, muscle bulk can only be increased through the hypertrophy of existing individual fibres that results from the creation of new myofibrils. This fact is just one reason why this organ system is relevant to discuss in the context of sport, doping and health side effects.

B Anabolic Androgenic Agents

The use of doping agents, and in this case anabolic androgenic steroids (AAS), is not limited to competitive sports. It has already spread to leisure sports including the fitness and bodybuilding area [1]. In spite of numerous reports on health risks associated with the use of AAS it still remains a widely abused drug and its popularity persists. AAS, synthetic derivatives of testosterone, produce
anabolic and androgenic effects. The androgenic effect pertains mainly to the development of male characteristics (virilisation) and the anabolic effect includes the stimulation of protein synthesis and inhibition of protein breakdown [2]. The proposed mechanisms of action being attractive in relation to athletic performance are the increase in skeletal muscle protein synthesis and skeletal muscle hypertrophy and the decrease in the rate of protein breakdown [3-6]. But as AAS are often used in supraphysiological doses the adverse effects cannot be neglected. The main adverse effects can be seen in the hepatic, cardiovascular, reproductive and endocrine, dermatological, and psychiatric systems (see specific chapters). But there are also some adverse effects reported in the musculoskeletal system, e.g. causing bone fractures, tendon pathology and rhabdomyolysis [7].

If applied in young athletes at children age, AAS induce a premature closure of the epiphysis resulting in growth retardation. Furthermore, a premature closure of the growth centres of long bones in adolescents can occur, which may result in the stunting of the linear growth [8,9].

The steroids, as well as having generalized effects, cause changes in the tendon structure itself, and this is compounded by intense exercise. This has been demonstrated earlier in animal models [10-13]. AAS appear to induce reversible changes in the biomechanical properties of tendon producing a stiff, less elastic tendon. The ultimate strength of the tendon is unaffected [12,14]. Although AAS increase tendon stiffness no AAS-induced structural or biochemical alterations have been found. Therefore, a strict distinction should be made between the loss of elasticity and an actual tendon rupture [12,14]. It is possible that the rapid strength adaptations being produced by AAS in skeletal muscle are not simultaneously accompanied by slower adapting, less vascular tendon structures, making tendons the weakest link in the chain [15].

The reports of tendon damage mostly occur among weight lifters, although ligament ruptures may be due to the excessive loads. The use of AAS concomitantly with exercise may lead to dysplasia of collagen fibrils, which can decrease the tensile strength of tendon. Changes in tendon's crimp morphology have been shown to occur as well. They may alter the rupturing strain of tendon and the normal biomechanics of the extremities. Altered arrangement and contractility of myofibrils and collagen fibres may lead to deterioration in plasticity [16]. In this context, a case of spontaneous rupture of the anterior cruciate ligament is reported in a bodybuilder taking steroids [17]. A current case report of a 29-year-old professional footballer abusing AAS for 3 years, showed a rupture of the patellar tendon and of both Achilles tendons within 18 months. After a ligament reconstruction with a semitendinosus tendon graft with
subsequent infection, the tendon and reserve traction apparatus were lost. Repeated warnings of impaired healing if anabolic use is continued had been neglected completely [18].

Rhabdomyolysis, or acute skeletal muscle destruction may occur after intake of anabolic androgenic steroids in combination with weight-training programmes [19,20], too. Taking the supraphysiological doses of steroids consumed by some athletes into account, these athletes are at a significant risk to exert a destructive effect to the integrity of their tissue.

C Hormones and Related Substances

The most important substances in this field associated with the supporting apparatus and the musculoskeletal system are the human growth hormone (hGH), the insulin-like growth factor (IGF-1), the gonadotrophins, and the corticotrophins.

The hGH is a peptide hormone secreted by the anterior pituitary gland and. It acts by binding to a specific growth hormone receptor, which is expressed by almost all human body cells [21]. The belief that hGH and thus IGF-1 can enhance performance led to the idea of abusing these substances in sports. The abuse by athletes and amateurs is based on the stimulation of the protein synthesis and thus the hypertrophy in muscle fibres. The effects of hGH intake described in controlled studies are often less impressive than anabolic effects reported by those who misuse this substance [22-24]. HGH activates tissues and liver cells to produce IGF-1 [25-28], thus the side effects occur through the actions of either hGH and IGF-1. The clinical version of an oversecretion of hGH in the pituitary gland is known as acromegaly [29]. The adverse effects seen in adults abusing hGH are the same as those of the clinical symptoms of acromegaly. The visible changes of bone and cartilage are amongst others the enlargement of hands and feet, nose, chin, tongue and ears. High hGH levels in the adult lead to hypertrophy and bone protuberances, sometimes irreversible, arthritis and induces acromegaly. The same side effects are noticed in children, but in addition gigantism can occur due to the increase in the linear growth of bone tissue. Reduced hGH levels in children result in dwarfism. Bone growth can be enhanced by hGH and IGF-1 as well as normal body growth and it can lead to osteoarthritis. For athletes, usually having normal levels of hGH, treatment with hGH essentially aims to raise blood levels above the normal value. This artificially creates a condition of hGH excess and leads to the above mentioned effects [25-31]. It is difficult to completely dissociate the biological
effects of hGH from those mediated through its target growth factor IGF-I. Therefore the adverse effects have to be seen as combined effects.

D Beta-2-Agonists

Although beta-2-agonists were traditionally used for the treatment for respiratory ailments, their abuse became prevalent for the purpose of enhancing performance. The ability to increase skeletal muscle mass and decrease body fat led to a high attractiveness among sportsmen [32,33]. Animal data reveal that 14 consecutive days of ingesting clenbuterol increases contractile strength of skeletal muscle. However, expressed per gram of muscle, power output was similar between animals receiving the beta-agonist clenbuterol and those receiving placebo. The authors, Dodd and colleagues, concluded that clenbuterol increased muscle strength and muscle size due to hypertrophy of both slow-twitch and fast-twitch fibres [34]. The respiratory agents have some adverse effects on the musculoskeletal function that shall be discussed briefly. They are based on a cascade of beta-agonists binding to beta-adrenoreceptors, which influence several metabolic and physiological processes in the skeletal muscle [35].

For instance, negative effects on the bone architecture of salbutamol-treated rats could be observed [36]. Bone loss occurred independently of a salbutamol-induced anabolic effect on muscle mass and was equally severe in sedentary and exercising rats. These results undermined the deleterious effect of beta-2-agonists on bone mass and bone mineral density during chronic treatment. Additionally, these effects were investigated on ovariectomized rats, i.e. rats with an estrogen deficiency. The negative effects on bone quality (femoral trabecula thickness) and quantity (femoral bone mineral density) were most significant in trained and ovariectomized rats and may indicate potential complications in doping female athletes with exercise-induced amenorrhea [37]. Furthermore, the effects of salbutamol and clenbuterol on bone were tested separately in female rats. The salbutamol and clenbuterol treated animals displayed lower bone mineral contents, femoral length and cortical width than the control animals. Clenbuterol treatment further reduced bone mineral density and the bone microarchitecture was clearly altered by clenbuterol. This was evidenced by lower trabecular number, connectivity and trabecular bone volume, leading to lower ultimate force. Both beta-2-agonists increased the bone resorption marker without any change of a bone formation marker. These results confirm again the deleterious effect of beta-2-agonists on bone mass
and show the negative effects of clenbuterol on trabecular bone microarchitecture. [38].

Excessive intake of beta-2-agonists can also lead to symptoms of muscle tremor and muscle cramps, especially observed with clenbuterol [33,39]. These effects are intensified by the simultaneous intake of diuretics, which is common among bodybuilders being near to a competition. Therefore, bodybuilder platforms recommend a potassium supplementation to improve the electrolyte balance and reduce the muscle cramping.

**E Diuretics**

The intention of abusing diuretics in sports is not because of an expected effect in performance enhancement but rather the control or loss of body weight. Bodybuilders for example use diuretics to achieve a better muscle definition due to the loss of water [40]. Furthermore, diuretics can be abused to dilute urine so that other abused doping substances cannot be detected. Common among all diuretics is hypohydration, which has been shown to have a variety of effects on performance, including impaired strength, power and endurance [41,42]. The adverse effects of diuretics on the musculoskeletal system are often secondary effects. Thus, effects like muscle cramps and pain are related to alterations of the resting electrical potentials in nerves and muscle membranes and their subsequent effects on the conduction of neuromuscular impulses. They are mostly based on the hypokalemia caused by the diuretics [43]. The potassium concentration levels in the serum can be correlated with specific clinical symptoms [41]:

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<th>Concentration (mmol/l)</th>
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<td>3.0–2.6</td>
<td>Tenderness or pain in muscles, occasional cramps</td>
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<td>&lt; 2.5</td>
<td>Muscle breakdown</td>
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<td>&lt; 2.0</td>
<td>Muscle cell death</td>
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Another potential risk of diuretic abuse by athletes is a deteriorated thermoregulation, based on the potentiated hypohydration effect of diuretics and sweat loss during exercise [44]. The increase in the body heat storage during exercise, due to a reduced sweating and skin blood flow coupled with electrolyte imbalances, especially potassium, can lead to serious health problems.
F Glucocorticosteroids

Glucocorticosteroids (GCs) are among the most potent and effective anti-inflammatory agents, with an unusually wide spectrum of activity. They are prominent in the treatment of a variety of acute and chronic inflammatory conditions, what makes them attractive for sports medicine. GCs are often administered locally by musculoskeletal problems as they can be injected in joints and around tendons and ligaments [45]. Corticosteroid injections are one of the most commonly used treatments for chronic tendon disorders as they lead to a rapid improvement of the symptoms [46,47]. But it is also discussed that this feeling of improvement can result in a premature exposure of the tendon. In the worst case this can imply the risk of a total tendon rupture [48,49].

The adverse effects of GCs can be compared to those of the anabolic steroids due to the affiliation of GCs to catabolic hormones. For instance, long-term abuse of glucocorticoids is associated with loss of bone and muscle mass [50]. Corticosteroids are the principal cause of secondary osteoporosis after a therapy. Doses of more than 5 mg daily and periods of treatment lasting more than 3 months increase the risk of osteoporosis and fragility fractures [51,52]. The trigger of this effects is a inhibited bone metabolism. Adverse effects like atrophies of tendon and ligaments were also reported in animal studies and case studies of humans [53-55]. Therefore, controversial opinions about the use of local corticosteroid injections for the treatment of Achilles tendonitis are existent. Some recommend the use of GCs based on efficacy in accelerating the healing process of Achilles tendonitis; others believe the associated side effects should preclude their use altogether. The decreased tendon strength seen upon intratendinous injections in animal studies suggests that rupture may be a potential complication for several weeks following injection and athletes should comply with a period of restricted training and sporting activity. In summary, GCs present severe side effects and risks on muscles, tendons and ligaments: starting with osteoporosis and the increased risk of fractures and a delayed bone repair up to a decrease in muscle nutrition and a severe risk of muscle atrophy.

G Beta-Blockers

Beta-blockers, also known as beta-adrenergic antagonists, are used to treat a variety of conditions, such as hypertension, tremor, anxiety and migraines. They bind to the surface of adrenergic receptors found throughout the whole body [56]. The main reason that beta-blockers are abused in sports is their effect to reduce anxiety and the associated increase in heart rate and skeletal muscle
tremor. Therefore, the abuse is located in the field of sports requiring precision like shooting events [57]. The beta-blocker metoprolol improved the pistol shooting performance by 13.4% compared with placebo referred to a decreased hand tremor [57]. The positive effects of beta-blockers in competition performance have also been detected in ski jumping, flying, motor car racing, parachute jumping and bob running [58]. Adverse effects of beta-blockers can be observed at an overdose or an abuse in healthy persons mainly located in the cardiovascular system. An adverse effect concerning the skeletal muscle can be seen in glycogenolysis, which is mediated by epinephrine via stimulation of beta-2 receptors. During submaximal exercise muscle glycogenolysis is unaffected, but the maximal glycogenolytic rate at high exercise intensities is decreased. [59].

H Conclusion
The reviewed scientific works show that some doping substances can seriously affect the musculoskeletal system and the supporting apparatus. These adverse effects are mainly located in bones, muscles, tendons, and ligaments and sometimes with irreversible effects. Every way of distribution of the above mentioned drugs to athletes with a non-medical intent has to be considered as unethical and irresponsible alike the abuse of these substances for doping purposes.

I References


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3.2 CARDIOVASCULAR SYSTEM

Asterios Deligiannis, Evangelia Kouidi

A Introduction

The abuse of doping substances has numerous cardiovascular side effects, which are deleterious for athletes’ health. The problem is that most of the athletes are using a variety of prohibited substances, in huge doses and for a long period of time. Therefore, it is difficult to isolate and specify the disorders that the abuse of a unique prohibited substance may cause. Additionally, the majority of the athletes refuse to admit that they are users and most of the side effects are not listed. Some of the prohibited drugs cause acute side-effects and may lead to sudden cardiac death, while others are associated with chronic adverse effects. The common cardiac side-effects of the most known substances are shown in table 1 [1], while the last WADA doping list of drugs affecting cardiovascular system is presented at the end of the article in table 2.

B Substances and Methods Prohibited at all Times

Androgenic-anabolic steroids (AASs)

Athletes usually use AASs to enhance athletic performance or to improve appearance. The side effects of AAS are many but unclear, mainly because it is difficult to isolate the side effects of the drugs used. Several cardiovascular adverse effects have been reported. Myocardial infarction and sudden cardiac death are the most serious complications of the abuse of anabolic steroids. Other common cardiovascular disorders are arterial hypertension, heart failure, cardiomyopathy, arrhythmias, thrombosis etc. [2-4].

According to Melchert and Welder there are four hypothetical models of anabolic-induced adverse cardiovascular effects [5]:

- An “atherogenic” model involving the effects of AASs on lipoprotein concentrations.
- A “thrombogenic” model involving the effects of AASs on clotting factors and platelets.
- A “vasospasm” model involving the effects of AASs on the vascular nitric oxide system.
- A “direct myocardial injury” model involving the effects of AASs on myocardial cells.
Table 1. Cardiac side effects of prohibited substances (adapted from A. Deligiannis et al. [1]). LVH: Left Ventricular Hypertrophy, CAD: Coronary Artery Disease, MI: Myocardial Infarction, HF: Heart Failure, SCD: Sudden Cardiac Death, AAS: Androgenic-Anabolic Steroids, hGH: Human Growth Hormone, EPO: Erythropoietin

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Many studies have demonstrated that AAS abuse in combination with resistance training cause concentric hypertrophy of left ventricular wall. The long-term use of AASs is found to cause an increase in myocardial mass and end-diastolic volume [6, 7]. However not only contractile but also non-contractile elements are increased. Generalized and focal fibrosis and myofibrillar disarray are also found in autopsy of athletes consuming large amounts of AAS [8, 9]. It is reported that AASs use does not improve left ventricular systolic function and may lead to diastolic dysfunction [6, 7]. There is evidence that AASs can generate dysrhythmias [5, 10]. AASs are found to affect the cardiac sympathetic nervous system and also electrolyte concentrations, which may lead to atrial or ventricular fibrillation [1, 11]. Sudden cardiac arrest related to adrenergic stress and documented by an extensive myocardial necrosis is also found in young athletes abusing AAS [4].
Use of AASs is found to lead to a significant decrease in high density lipoprotein (HDL) cholesterol and an increase in low-density lipoprotein (LDL) cholesterol [12]. However, AAS abuse may cause a beneficial effect on Lp(a) levels [12]. The duration of AAS intake seems to affect the lipids level, rather than the dosages [12]. Decreased fibrinolytic activity and increased clotting factors have been reported after AAS abuse causing thrombotic phenomena [13]. Bodybuilding is found to be associated with impaired vascular reactivity and increased arterial thickening regardless of AAS use [14]. It is also supported that AAS and particularly androgens may increase either systolic or diastolic blood pressure [15].

**Peptide hormones, mimetics and analogues**

Growth hormone (hGH) appear direct anabolic effects, it increases insulin levels, which exerts an antiproteolytic effect, possibly leading to short-term increase of physical performance [16]. However, long-term use of hGH is found to cause cardiomyopathy, and increase the incidence of arrhythmias [17].

Erythropoietin (rHuEPO) is mainly used by endurance athletes, in order to increase their aerobic capacity. Treatment with rHuEPO leads to a dose-dependent increase in hematological parameters. It increases red blood cell mass and can also elevate the levels of Hb and Hct, when it is repeatedly administered [18]. High levels of Hct may cause increased viscosity of the blood, which elevates the risk of thrombosis and embolisms [19]. Moreover, arterial hypertension and seizures may be observed [20]. A significant decrease in maximum heart rate is also been reported [18].

**Beta-2 agonists**

Beta-2 agonists such as clenbuterol and salbutamol, may increase muscle mass and decrease fat. Clenbuterol leads to increased heart rate, cardiac output and cardiac oxygen demands. Beta-2 agonists abuse may lead to arrhythmias, myocardial ischemia, congestive heart failure, prolonged QT interval and sudden cardiac death [21].

**Diuretics**

Athletes usually use diuretics either to reduce body weight or to mask drug contents in the urine. The intake of diuretics may cause electrolytic imbalance
and particularly hypokalaemia. Hypotension, prolonged QT and arrhythmias are also observed after administration of diuretics [22].

C  Substances and Methods Prohibited only in Competition

Stimulants

There may be an improvement of exercise performance when taking amphetamines, due to their ability to mask fatigue. Amphetamine abuse may lead to arterial hypertension, cardiac arrhythmias, acute myocardial infarction, cardiogenic shock and sudden cardiac death [23].

Cocaine doesn’t seem to affect athletic performance. However, its use causes myocardial ischemia and coronary artery thrombosis and myocardial infarction. These disorders are the result of vasoconstriction and stimulation of α-receptors, as well as of increased myocardial oxygen demand, decreased oxygen supply and ingressive thrombogenesis [24,25]. Other cardiovascular side effects of cocaine use include infective endocarditis, ruptured aortic aneurysm, vascular thrombosis, coronary vasospasm, arterial hypertension and stroke [24,25]. Moreover, cocaine may cause myocarditis and dilated cardiomyopathy. Chronic cocaine abuse leads to myofibrial necrosis, interstitial fibrosis and congestive heart failure [26]. Cocaine abuse may cause prolonged QT and PR intervals and A-V conduction disorders. It increases the cardiac sympathetic activity by stimulating the β-receptors and inhibits the cardiac ion channels acting as local anesthetic. Sudden cardiac death may occur due to adrenergic overactivity and lethal arrhythmias [27].

Ephedrine-containing preparations may increase energy levels, produce euphoria, aid to weight loss and improvement of muscle mass. Bodybuilders show a high incidence rate for ephedrine abuse. There is evidence that ephedrines cause cardiac stimulation and an increase of systolic and diastolic blood pressure [28]. Other cardiovascular adverse effects of its use are cardiac arrhythmias, acute myocardial infarction and sudden cardiac death [29]. Constriction of coronary arteries and vasospasm are thought to be the mechanisms of myocarditis and myocardial infarction after ephedrine administration. They may also cause ischemic stroke as a result of vasoconstriction of cerebral arteries and hemorrhagic stroke following the hypertensive action of ephedrine [29].
Narcotics
The use of narcotics is not ergogenic. Especially narcotic analgesics use can be harmful when an injured athlete participates in a sport activity. The use of morphine, heroin or codeine may affect blood pressure and cause acute pulmonary edema, coma and death [30].

Cannabinoids
Cannabinoids can reduce anxiety, but do not have an ergogenic effect. They possibly cause a parasympathetic blockade. Moreover, they produce β-adrenergical stimulation leading to increased heart rate and decreased cardiac output [31]. Its use may increase the myocardial oxygen demand, as well as decrease oxygen delivery, as a result of arterial vasospasm. These alterations lead to myocardial ischemia, arrhythmias, and sudden cardiac death [31]. Cannabis may also cause changes in ST-segment, T-wave and flattening of P-wave. There are also published cases of stroke after smoking cannabis [31].

Glucocorticosteroids
Arterial hypertension is the most serious side effect of high doses and prolonged intake of glucocorticosteroids [32]. Oral or parenteral administration of glucocorticoids is found to be a significant risk factor for hypokalaemic events [33]. Other side-effect is dydlipidemia, caused by increased plasma insulin levels and disorders of lipid metabolism.

D Substances Prohibited in Particular Sports
Alcohol
Alcohol does not have an ergogenic effect. Long-term alcohol consumption may lead to arterial hypertension, cardiac arrhythmias, ischemic heart disease, dilated cardiomyopathy, stroke and sudden cardiac death [25,34]. Moderate alcohol consumption is a common cause of secondary hypertension, more often systolic than diastolic. Alcohol use causes increased cardiac sympathetic activity, leading to tachycardia and increasing the risk for ischemic heart disease and atrial, mainly, arrhythmias. However, moderate drinkers may have low LDL and high HDL levels, which decreases the incidence of coronary atherosclerosis.
Beta-blockers

B-blockers are mainly used in sports that require accuracy, since they are found to reduce anxiety and tremor. However, they are found to decrease physical capacity. Their use may cause demonstrable reduction of heart rate and blood pressure [35].

E Prohibited Methods

In the prohibited methods, the following categories are included: Enhancement of oxygen transfer, pharmacological, chemical and physical manipulation and gene doping. From these methods, only blood doping is reported to cause adverse cardiovascular effects.

Blood doping leads to increased red blood cell mass and thus to increased physical capacity. Increasing the heart rate and the cardiac afterload may cause arterial hypertension, myocardial infarction and heart failure [20].

F Combination of Prohibited Substances

In practice, most of the athletes use a combination of the above mentioned substances or methods, which usually have synergic action.

There is a report of a bodybuilder taking AASs, amphetamines, diuretics and potassium supplements and collapsed with a run of ventricular tachycardia and myocardial infarction [10].

Combination of ephedrine and caffeine, which are mainly used in herbal dietary supplements are found to produce significant cardiovascular, metabolic and hormonal responses and cause seizures, strokes and death [36]. They produce both chronotropic and vasopressor responses and increase both blood pressure and heart rate. Increased cardiac sympathetic activity may lead to myocardial ischemia and induce cardiac arrhythmias. Their effects seem to be a result of pharmacodynamic interactions [36].

Historically, 102 different substances were detected in the body of Brigit Dressel, who died due to an anaphylactic shock in 1987 and a huge number of prohibited substances were found in the personal diary of Andreas Münzer, whose death was also due to doping substances abuse.

Finally, the cardiovascular side effects of prohibited substances and methods depend on the amount and combination of the consumed drug, the duration of use and the counteractions of each athlete.
Table 2. WADA doping list of drugs with cardiac side effects (adapted from A. Deligiannis et al. [1])

<table>
<thead>
<tr>
<th>Prohibited in competitive sports</th>
<th>Prohibited in certain competitive sports</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulants:</strong></td>
<td><strong>Beta Blockers:</strong></td>
</tr>
<tr>
<td>amphetamine</td>
<td>atenolol</td>
</tr>
<tr>
<td>cocaine</td>
<td>bisoprolol</td>
</tr>
<tr>
<td>ephedrine</td>
<td>carvedilol</td>
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<tr>
<td>fencamfamin</td>
<td>esmolol</td>
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<tr>
<td>modafinil</td>
<td>labetolol</td>
</tr>
<tr>
<td>nikethamide</td>
<td>metoprolol</td>
</tr>
<tr>
<td><strong>Narcotics:</strong></td>
<td><strong>Beta Blockers:</strong></td>
</tr>
<tr>
<td>morphine</td>
<td>pindolol</td>
</tr>
<tr>
<td>pethidine</td>
<td>propranolol</td>
</tr>
<tr>
<td><strong>Beta-2-agonists:</strong></td>
<td>sotalol</td>
</tr>
<tr>
<td>reprotoerol</td>
<td></td>
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<tr>
<td>isoprenaline</td>
<td></td>
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<tr>
<td><strong>Masking Drugs (Diuretics):</strong></td>
<td></td>
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<tr>
<td>amiloride</td>
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<tr>
<td>chlortalidone</td>
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<tr>
<td>etacrynic acid</td>
<td></td>
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<tr>
<td>furosemide</td>
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<td><strong>Anabolic Steroids:</strong></td>
<td></td>
</tr>
<tr>
<td>testosterone</td>
<td></td>
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<tr>
<td>nandrolone</td>
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<tr>
<td>stanozolol</td>
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<tr>
<td>metandienone</td>
<td></td>
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<tr>
<td><strong>Glucocorticosteroids:</strong></td>
<td></td>
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<tr>
<td>betamethason</td>
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<tr>
<td>triamcinolon</td>
<td></td>
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<tr>
<td><strong>Peptide Hormones:</strong></td>
<td></td>
</tr>
<tr>
<td>human growth hormone</td>
<td></td>
</tr>
<tr>
<td>erythropoietin</td>
<td></td>
</tr>
</tbody>
</table>
G References


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3.3 RESPIRATORY SYSTEM

Katerina N. Georgieva

A Anabolic Androgenic Steroids

Misuse of the synthetic derivatives of the testosterone, the anabolic androgenic steroids (AAS), causes serious side effects on several functional systems of athletes [1]. Little data are available about the side effects of AAS use on respiratory system. Some studies associate androgen administration with a higher risk of occurrence or exacerbation of the sleep apnea syndrome [2-4]. In general, sleep apnea is a phenomenon of recurrent cessation or decrease of airflow to the lungs during sleep. Sleep apnea, considered to be at least 5 episodes of apnea/hypopnea lasting at least 10 sec of every sleep hour, is classified as either central, due to cessation of respiratory movements, or obstructive due to narrowing of the upper respiratory airways [5,6]. A combinations of these two conditions leads to mixed sleep apnea. The repetitive episodes of apnea occurring during the sleep are associated with severe intermittent hypoxia and sleep fragmentation. The symptoms include morning headaches, fatigue and in more advanced cases – clinical picture of respiratory failure. Sleep apnea is a common cause of snoring, daytime sleepiness, impaired cognitive performance and road traffic accidents. It also has been shown to predispose to ischemic heart disease, arterial hypertension and cerebrovascular accidents [5,7]. The sleep apnea syndrome is more common in men than in women and testosterone is thought to play a role in the pathogenesis of the sleep apnea. Recent data suggest that endogenous testosterone affects the ventilatory response to chemoreceptor stimulation during wakefulness and sleep in young healthy males [8].

Androgen administration may induce or exacerbate obstructive sleep apnea in some men [2], women [3] and children [4]. Consistent with these observations are recent results demonstrating a reduction in total sleep time, longer hypoxic episodes and increases in the respiratory disturbance index (the number of apneas and hypopneas per hour) in healthy older men exposed to high doses of testosterone esters [6]. Increased endogenous testosterone production as a result of testosterone-producing tumor also may induce obstructive sleep apnea in women [9]. The possible mechanisms of this effect of androgens are associated with an increase in the upper airway collapsibility and influence on the neuromuscular control of upper airway patency during sleep, [4] as well as to a reduction in upper airway dimension following the anabolic effect on the structural configurations of the oropharynx, especially in women [3].
B Growth hormone and Insulin-like growth factor-1

Growth hormone (GH) is used in sport because of its anabolic and lipolytic effects [10]. While its effectiveness in enhancing physical performance is still not proved, recent data show that high doses of GH given to healthy subjects and endurance athletes lead to glucose intolerance and insulin resistance, significant alterations in iodine-containing thyroid hormones levels, and increased insulin-like growth factor-1 (IGF-1) concentrations [11,12]. The long-term health effects of GH use in athletes are not well known but acromegalic patients with chronic endogenous GH excess may serve as the most accurate model for an athlete supplementing an already normal hormone level [10]. Prolonged exposure to elevated endogenous levels of GH and IGF-1 results in both direct structural and functional tissue damage and the development of secondary systemic disorders. The clinical manifestations of acromegaly range from subtle signs of acral overgrowth, soft-tissue swelling, arthralgias, and fasting hyperglycemia to florid osteoarthrosis, diabetes mellitus, goiter, hypertension, and cardiac and respiratory failure [13,14].

Patients with acromegaly develop several respiratory alterations as a consequence of the hypertrophic action of GH and IGF-1 on craniofacial bones and soft tissue, respiratory mucosa/cartilages, lung volumes and activity of respiratory muscles (Tab. 1.) This range of abnormalities results in sleep apnea and impaired respiratory functions. In the upper airways, remodeling of bones and soft tissues results in the impairment of normal pharyngeal patency during sleep and is a key to the onset of obstructive sleep apnea, the prominent type of sleep breathing disorder in acromegaly. Chronic GH excess causes several alterations which may contribute to impairing the intrapharyngeal balance during inspiration and thus increase pharynx collapsibility during sleep [14,16]. About one third of acromegalic patients develop mixed sleep apnea [18]. Sleep apnea may affect as many as 80% of acromegalic patients and is apparently more frequent and severe in case of elevated GH/IGR-1 levels and male gender [14].
Table 1. Chronic GH excess induced morphological and functional alterations related to respiratory system dysfunction [13, 14, 15, 16, 17].

<table>
<thead>
<tr>
<th>Site</th>
<th>Pathological findings</th>
<th>Clinical disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial region and upper respiratory</td>
<td>Macroglossia</td>
<td>Impaired airflow transit</td>
</tr>
<tr>
<td>airways</td>
<td>Swelling of the soft palate</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td></td>
<td>Swelling/collapse of the pharyngeal walls</td>
<td>Nocturnal snoring</td>
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<tr>
<td></td>
<td>Thickening of vocal cords</td>
<td>Fragmented sleep</td>
</tr>
<tr>
<td></td>
<td>Overgrowth and protrusion of mandible, overgrowth of maxilla</td>
<td>Daytime somnolence</td>
</tr>
<tr>
<td></td>
<td>Thyroid overgrowth</td>
<td></td>
</tr>
<tr>
<td>Thoracic cage, lower respiratory airways</td>
<td>Small airway narrowing</td>
<td>Impaired airflow transit</td>
</tr>
<tr>
<td>and lungs</td>
<td>Derangement of respiratory muscles</td>
<td>Stiffened rib cage</td>
</tr>
<tr>
<td></td>
<td>Enlargement of vertebral bodies</td>
<td>Impaired breathing movement</td>
</tr>
<tr>
<td></td>
<td>Elongation and divergence of the ribs</td>
<td>Respiratory muscle impairment</td>
</tr>
<tr>
<td></td>
<td>Lung overgrowth</td>
<td>Short inspiratory time</td>
</tr>
<tr>
<td></td>
<td>Increased lung volume</td>
<td>Emphysema</td>
</tr>
<tr>
<td></td>
<td>Increased lung compliance</td>
<td>Bronchiectasis</td>
</tr>
</tbody>
</table>

Impaired respiratory function originates from the alterations involving the bone, muscle structure of the chest and in lung volume and elasticity. In the lungs proliferations of pneumocytes and smooth muscles cells is reflected in the overgrowth of pulmonary epithelium and thickening of interstitial tissue. This alteration decreases pulmonary elasticity, whereas lung volumes are increased due to alveoli overgrowth [14,15]. This process leads to respiratory dysfunction; the ventilatory response on effort is frequently inadequate in the face of a greater effort as well as the sense of physical exhaustion. Respiratory mortality appears to be 3-fold higher in acromegalic patients than in normal subjects [14].

C Stimulants

Central nervous system stimulants, such as amphetamines and cocaine, are usually used by athletes to improve performance on the day of competition. The
beneficial effects of amphetamines on exercise performance appear to result from masking pain and/or fatigue. Cocaine increases tolerance to intense exercise, but most of its chronic effects on energy metabolism are negative. Amphetamine misuse may carry significant risk for the athletes as evidenced by several amphetamine-linked deaths in sport. A number of dramatic fatalities have also occurred in athletes misusing cocaine [19]. Acute and chronic abuse of these stimulants may result in significant neurologic, cardiac, psychiatric, obstetric and respiratory complications. The severity and variability of stimulant-induced pulmonary toxic reactions appears to depend on the compound used, the dosage and the route of administration [20,21].

Cocaine

Acute pulmonary symptoms of smoking cocaine include cough, black sputum, hemoptysis and pleuritic chest pain. Smokers of crack cocaine with chest pain have higher carboxyhemoglobin levels and this may play a role in nonpleuritic cocaine-related chest pain [22]. The use of freebase cocaine has been associated with barotraumas. Pneumothorax, pneumopericardium and pneumomediastinum are the common manifestations of cocaine-induced barotraumas. Smoking of cocaine is also associated with asthma-like symptoms, exacerbation of asthma and various airway complications including sinusitis, epiglottitis, bronchitis, and obliterative bronchiolitis. In addition, hot cocaine vapours may cause thermal burns of the respiratory tract [20,23]. Research has found decreased diffusion capacity of the lungs reflecting reduced alveolar-capillary interface that lasts weeks to months after cocaine exposure. The proposed mechanism of this reduction is vascular abnormalities [20]. Crack use is associated with the syndrome of “crack-lung”, characterized by diffuse alveolar infiltrates, pulmonary and systemic eosinophilia, fever and respiratory failure. It occurs within 1 to 48 hours after heavy cocaine smoking. Pulmonary alveolar hemorrhage, hemoptysis with and without pulmonary infarction are frequently reported with cocaine abuse. Cocaine use also induces acute noncardiogenic pulmonary edema [20,23,24]. Possible mechanisms include local cellular toxic reactions and microvascular pulmonary effects. Stimulation of the central nervous system to induce noncardiogenic or neurogenic pulmonary edema is also postulated. Stimulants generally cause respiratory stimulation, but severe overdose may lead to respiratory depression. Animal models of cocaine poisoning suggest that postictal respiratory depression or, in the absence of seizures, direct respiratory depression plays a major role in the mechanisms of cocaine-induced death [25,26]. Chronic cocaine use can induce foreign body granulomas, interstitial pneumonitis and
fibrosis, and pulmonary hypertension. It is suggested that prenatal exposure of cocaine increases the risk of sudden infant death syndrome [20].

Amphetamines

The effects of amphetamine intoxication on respiratory system include dyspnea, asthma exacerbation, bronchitis, and acute noncardiogenic pulmonary edema [20,21]. Panlobular emphysema with granulomas is observed in intravenous abusers of methylphenidate [27]. Pulmonary hypertension has long been reported in amphetamine users. Contaminants have been suggested as the cause of pulmonary hypertension after methamphetamine inhalation, although a direct role of the stimulant is not excluded [21].

D Narcotics

Narcotics are naturally occurring, semisynthetic or synthetic drugs which bind to opioid receptors to produce physiological effects and which are antagonized by naloxane. The main use of opioids in medical practice is in the treatment of moderate-to-severe pain. Most of the current available opioid analgesics exert their analgesic and adverse effects primarily through the opioid mu-receptors. The clinical use of the opioids is limited by serious side effects such as respiratory depression, development of tolerance, and psychological and physical dependence. Excessive dosing of opioids may results in significant toxicity. The toxic and lethal doses depend greatly on the individual's tolerance to the drug, thus the usual dose for an addict is dangerous for a nonuser or may be dangerous for the same addict after several days of abstinence because of the rapid diminution in tolerance. The main toxic effects are respiratory depression, coma and death [28-30].

The respiratory system is the commonest site of complications of opioid overdosage. The effects include respiratory depression, acute pulmonary edema, bronchospasm, aspiration of vomit and aspiration pneumonia. Death from opioid overdose is usually due to respiratory failure [31]. Respiration is controlled through medullary respiratory centers with peripheral input from chemoreceptors and other sources. Opioid administration leads to respiratory depression because it produces inhibition at the chemoreceptors via mu-opioid receptors and in the medulla via mu- and delta-receptors [29]. Reduction in the ventilation (at end-tidal Pco₂), increase in the resting and tidal CO₂, and a rise in the CO₂ threshold are observed in healthy subjects after opioid administration [32, 33]. The effect on respiration depends on the type of the opioid agonist. For
example, in opioid-naïve volunteers morphine and fentanyl (pure agonists) produce dose-dependent depression of minute ventilation with apnea at high dose levels, but buprenorphine (partial agonist) causes dose-independent respiratory depression with a ceiling effect at higher doses [34, 35]. Independent of the type of the opioid, the opioid–induced respiratory depression leading to hypoventilation and hypoxemia may produce irreversible neurologic injury and this combined with the central nervous system depression may result in death [36]. Concurrent use of opioids with alcohol or benzodiazepines increases the risk of respiratory arrest. Glutamate and gamma-aminobutyric acid (GABA) are the major excitatory and inhibitory neurotransmitters, respectively, that mediate the control of respiration. This explains the potential for interaction of opioids with benzodiazepines and alcohol. Both benzodiazepines and alcohol facilitate the inhibitory effect of GABA, while alcohol also decreases the excitatory effect of glutamate on respiration [29]. Opioid overdose may also induce noncardiogenic pulmonary edema and bronchospasm. Pulmonary edema is almost universal occurrence in fatal overdose. Direct toxic effects or anaphylactoid reactions have been suggested as possible mechanisms of the opioid-induced noncardiogenic pulmonary edema [37, 38, 39]. Opioids have a histamine-releasing effect, which can also cause constriction of bronchial smooth muscles and induce bronchospasm and asthma exacerbation [40, 41]. In addition, opioids can cross the placenta and can be found in breast milk. Therefore, neonatal respiratory depression can occur in babies born to mothers addicted to opioids.

E Cannabinoids

Cannabis preparations contain more than 60 cannabinoids, but the major psychoactive component of cannabis is tetrahydrocannabinol (THC). Some of the most serious adverse effects of cannabis (marijuana) smoking are on the respiratory system. For the adverse effects of cannabis smoke on the lungs, effects of THC are perhaps of less importance than the numerous products of combustion to which smokers are exposed. Evidence suggests that the range of adverse effects on the lungs exerted by smoking cannabis is similar to those induced by tobacco smoking. Both the gaseous and the particulate phases of tobacco and cannabis smoke contain a similar range of harmful chemicals (“tar content”, carcinogens). However, the pulmonary consequences of cannabis smoking may be magnified by the greater deposition of smoke particulates in the lung due to the differing manner in which cannabis is smoked. Smokers typically inhale deeply and hold their breath to ensure maximum absorption of THC [42]. Studies demonstrate that airway inflammation develops even after
limited exposure to cannabis smoke. While THC causes modest short-term bronchodilation, cannabis smoke produces a number of long-term pulmonary changes including histopathological evidence of acute and chronic bronchitis. Symptoms of chronic cough and sputum production, and exercise-related dyspnea are common in cannabis smokers [43]. Habitual marijuana smoking is associated with abnormalities in the structure and function of alveolar macrophages potentially predisposing to pulmonary infection [44].

Cannabis smoke is carcinogenic in vitro and in vivo and is a possible cause of respiratory cancers in regular cannabis smokers. The same histopathological and mutagenic changes thought to be precursors of lung carcinoma have been found in the lungs of chronic cannabis smokers. Case reports have also documented cancers of the upper aerodigestive tract (mouth, tongue, and esophagus) in young adults who have been chronic cannabis smokers, but evidence from epidemiological studies is inconsistent [45].

F Beta–Blockers

Beta-blockers block the action of catecholamines on beta-adrenergic receptors. Asthma is a disease which is characterised by recurrent episodes of bronchospasm with periods of essentially normal lung function. Inhaled or injected beta-agonists cause bronchodilation (via beta 2-adrenergic receptors) and are used in the management of asthma. Therefore, use of (nonselective) beta-blockers may exacerbate or trigger bronchospasm in athletes/patients with asthma or pulmonary disease associated with hyper-reactive airways [46].

G Conclusion

There are little data available about the side effects of doping substances on the respiratory system of athletes. Anabolic androgenic steroids and GH/IGF-1 can provoke and/or exacerbate the obstructive sleep apnea, which can be partially attributed to their anabolic action. The airways and lungs can be seriously impaired by cocaine and cannabis smoking. Overdosage of stimulants and narcotics leads to respiratory depression, pulmonary edema and bronchospasms which may often have lethal outcome. On the basis of the research we reviewed we can conclude that some doping substances can exert serious life-threatening side effects on the respiratory system of athletes.
H     References


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3.4 GASTROINTESTINAL TRACT AND LIVER

*Carl Müller-Platz, Tsuyuki Nishino, Hande Sarikaya*

**A Introduction**

The digestive system is the organ to absorb and utilize food and also to egest indigestible substances. Digestive system disorders affect quality of life and decrease performance in and out of competition. Gastrointestinal diseases are often tedious due to constant stress of this organ.

**B The Digestive System**

The digestive system is a mucosa lined passage in which the ingested food will be broken up and subjected to mechanical and chemical processes. The nutrients will be resorbed, the indigestible residues will be egested as faeces.

Morphologically, the digestive system is regarded as a hose-like antrum, which is encircled by the mucosa with cells of different types and functions. In profile, connective tissue including capillaries and adenoids surrounds the tract while the longitudinal and circular musculature defines the outer boundary.

The directed transport of the food through the tract results from coordinated movements of the muscular layers, the peristalsis. The digestive system can be divided into different functional sections.

*The upper digestive part*

After ingestion, the food will be hackled by the teeths and prepared for further transport by saliva. The enzyme ptyaline, which is already present in the saliva, breaks down carbohydrates into smaller components. The mucosa around the oral cavity is able to resorb different substances. This fact is also used in the medical therapy. Through the oral cavity and the pharynx the mechanically hackled food reaches the esophagus. With the swallowing the volitional control ends and the digestive apparatus is subjected by autonomous nervous systems. The esophagus itself carries the food by strong peristaltic movements into the stomach. A further processing of the food does not take part in this section of the upper digestive tract. A ring-shaped muscle at the end of the esophagus causes the food intake into the stomach in portions.

In the stomach the food is further digested chemically by hydrochloric acid and biochemically by enzymes. Different cells of the stomach mucosa secrete
gastric juice, parietal cells hydrochloric acid, chief cells pepsinogen and mucous neck cells mucus. In the musculature of the stomach a wavelike contraction will be initiated by the so-called Cajal cells.

**Figure 1.** The gastrointestinal tract and main innervations, ENS: Enteric Nervous System, ANS: Autonomic Nervous System.

The small intestine

From the stomach the chyme reaches the duodenum through the pylorus. The bile duct and the excretory duct of the exocrine part of the pancreas also discharge into the duodenum. The exocrine part of the pancreas secretes digestive enzymes. From the gall bladder the bile coming from the liver will be stored and delivered. The jejunum and the ileum follow the duodenum. In these parts of the bowel enzymes and neuroactive substances are released. Enterochromaffin cells, which liberate the transmitter serotonin, are important for the control of the musculature and the secretion. Other cells secrete digestive enzymes. Additionally, intracellular enzymes are liberated by stalled upper mucosa cells.

The food is mixed by contraction of the bowel muscle layers, while contact with the mucosa is optimized and the chyme is transported along by peristaltic movements. The nutrients are resorbed by the mucosa and get into the
bloodstream and the lymphatic channels. The non absorbable parts of the food and the dietary fiber remain in the bowel.

![Figure 2. The cross section of the small (a) and large (b) intestine](image)

**The colon**

Below the junction of the small intestine the colon closes with a blind ended tube, the vermiform appendix. Above the junction the ascending colon travels up mostly along the right side of the body. The next section of the colon is termed the transverse colon due to it running across the body horizontally. Then, the descending colon turns downward and becomes sigmoid, which transports the indigestible rest of the food into the rectum. In the rectum the excrements will be collected and rectal tenesmus will be activated. The rectal tenesmus is controlled by the voluntary motor function. The most important task of the colon is the absorption of water and electrolytes and the increase of slippage of the indigestible rests.

**Liver, gall bladder and exocrine pancreas**

The liver is the most important organ for the metabolism and detoxication. The gall bladder is attached to it. The liver is a highly perfused organ, which cells are arranged to have intensively contact to the bloodstream. During metabolic processes the liver produces bile, which is important for the fat digestion. Main types of the liver cells are the parenchyma cells of the metabolic tissue, the stromal cells as supporting connective tissue and the so-called Kupffer cells for phagocytosing extraneous particles.
Furthermore, amino-acids are metabolized in the liver, glycogen is formed and it is the central organ for fat metabolism. The liver produces clotting factors and regulates the acid-base balance, vitamins and trace elements.

In the gall bladder the bile is stored, which is mainly produced by the hepatocytes of the liver, and then delivered into the duodenum. There is a feedback on the composition of the chymus via chemoreceptors which regulates the released amount of bile.

Liver and gall bladder are controlled differently. While the liver is controlled sympathetically and parasympathetically [1], the gall bladder is controlled by the enteric nervous system (ENS). The ENS also controls the exocrine part of the pancreas. The pancreas is divided into an exocrine, digestive orientated and an endocrine metabolism orientated part. The exocrine pancreas releases through the ductus pancreaticus further digestive enzymes (e.g. chymotrypsin) into the lumen of the duodenum. With its hormones insulin and glucagon the endocrine part mainly controls the glucose metabolism.

The enteric nervous system (ENS)

In the year 1897 Dogiel discovered neurons in the abdominal cavity, which he divided into three types according to their structure. He placed the cadre for the ENS which is comparable in its dimensions with the spinal cord. This nervous system controls the intestinal motility, secretion and absorption [2]. The ganglions are located in the intestinal wall. The Plexus Myentericus (Auerbach) is situated between the longitudinal and circular layers of muscle in the Tunica Muscularis and exerts control over the muscle tonicity and the intestinal motility. The Plexus Submucosus (Meissner) controls the secretory sequences and is located in the submucous coat of the intestine and contains ganglia from which nerve fibers pass to the mucous membrane. The high number of receptors consisting of afferent, sensoric and efferent pathways is responsible for often unspecific biomedical side effects on the digestive system.

The signal conduction of the ENS is similar to the vegetative nervous system (VNS), mainly working via acetylcholin and noradrenalin. The release of these neurotransmitters is modulated via several co-transmitters which react mostly at presynaptic located receptors [3]. Substances docking at these receptors are for example kinines, substance P or serotonin [4,5]. The VNS exerts direct influence up to the stomach and from the colon on. In animal experiments alpha- and beta-adrenergic receptors were detected in different densities based on the sections [6].
Since ghrelin was detected in the stomach of rats the knowledge on the food intake control mechanisms and energy balance has improved dramatically. Ghrelin causes with other mediators the appetite which leads to food intake. In fasting state and after food intake, the effect patterns between intestinal motility and secretion in the particular parts of the digestive tracts can be identified and assigned. Ghrelin also stimulates the excretion of human growth hormone via gastric afferent parasympathetic nervous pathways. Using the neuropeptide Y it stimulates the food intake [7]. In animal studies, the motor activity of the duodenum in saturated animals after application of ghrelin shows similar patterns like conditions before food intake [8].

Currently, 20 neuronal transmitters and other hormone-like substances are identified, whose interactions are under investigation in this system.

C Biomedical Side Effects of Doping Substances

The ENS reacts on many stimuli from the intestinal tract (mechanical and chemical receptors). Co-transmitters affect and modulate the signal transmission pre- and postsynaptically. In addition, further indirect influences of the sympathetic and parasympathetic nervous system have to be added. Systemic health side effects of doping active substances on the digestive tract are to be expected always then, when the active substance has an effect on this ENS, on the lymphatic or the circulatory system. Besides, it can lead to hormonal effects in target cells of the mucous membrane and the smooth musculature.

Actually, doping substances are drugs and thus developed for the therapy of illnesses. Besides desired therapeutic effects, undesirable side effects occur, whose appearance and frequency is investigated within the scope of the clinical test to healthy volunteers. These data, which would be especially appropriate for the consideration of the abuse by competitive athletes, are seldom available. After the commercial launch as a pharmacological drug of different galenics further messages about side effects emerge. This spectrum of side effects is dependent on the description and on the respective clinical picture of the treated patient. Just in the digestive tract side effects are mainly unspecific and appear often already as a concomitant of the illness, from incompatibility or, however, from other cause. In the end, psychosomatic influence has to be taken into consideration. Indeed, the side effects which are to be announced within the scope of the drug vigilance within the therapeutic application are taken up in their frequency, nevertheless, about the origin there are only very seldom investigations.
Hence, in the following consideration such side effects are only mentioned if their frequency lies in the percent area and, hence, a causal connection with the active substance can be supposed.

Side effects of the liver originate almost exclusively in cytotoxic mechanisms. The liver cells are overtaxed, die or the functional cellular tissue alters itself degenerative into connective tissue, inclusions or cancer cells.

In the clinical picture changes in the metabolism and linked illness symptoms are detected. A special importance comes up with the origin of liver damages to the so-called oxydative stress. This process leads to increased emission of free radicals, which can attack the cell at different places and lead to damages up to cell death. Signs of liver tissue damage are the increases of the concentration of hepatocyte specific enzymes in blood, hepatitis and icterus.

The health side effects of the active substances from the list of prohibited substances and methods are demonstrated in the following, according to the systematics of the 2007 WADA list.

S1. Anabolic active substances

Here, two kinds of substances are distinguished, anabolic androgenic steroids and other anabolic active substances using other mechanisms.

The androgenic-anabolic steroids (AAS)

The AAS are derivatives of the male gender hormone testosterone. The development of derivatives served the improvement of the pharmacokinetics and the change of the active spectrum for the amplification of one of the always together appearing androgenic and anabolic effect. Many derivatives have not overcome the hurdle of the bioassays for the clinical test, nevertheless, are to be purchased from different, mostly forbidden sources. Their specific side effects on the gastrointestinal tract are not known, presumably they may be like those of the admitted preparations.

In many investigations, mostly as surveys in fitness studios [9] admit between 10-40% of the interviewees the abuse of anabolic steroids. In a survey with 253 fitness studio customers 6% complained about diarrhea, 4% have declared changed faeces. About 30% of the drug abusing candidates reported an increased appetite during the intake cycles, which is probably released central nervously and hormonal, as the protein buildup requires additional nutrients. This symptom reverses beyond the intake cycles by 25% of the interviewed
persons in a loss of appetite and is accompanied in about 10% by feeling of nausea.

The effect of anabolic steroids on the gastrointestinal tract can be explained partly by the metabolic ways. Thus, the oversupply of anabolics leads to a partly conversion of those in estradiol by the enzyme aromatase. In animal experiments estradiol has a detectable influence on the intestinal functions, already in low concentrations. The threshold of these effects is increased by the pressure receptors, which initiate the peristaltic movement [10], and the defaecation of the intestine delays [11].

Anabolic steroids have an affinity to the androgen receptors whose stimulation causes a momentary hyperglycemia which leads to motility disturbances in the whole intestinal area. Acute effects from testosterone on the gastrointestinal tract are often nausea and vomiting, as well as loss of appetite and diarrhea. An oral application with longer whereabouts of the preparation in the oral space local inflammations are also reported what probably allows suggesting more on an allergenic reaction. Contact of testosterone with the skin can also cause irritations. In some cases severe side effects like stomach bleeding or bleeding of existing esophagus varices are reported. The latter has probably to be seen in close connection with other side effects like liver toxicity and blood pressure increase. With testosterone undecanoate side effects like indigestion and diarrhea are also described.

Nandrolone and oxandrolone are similar in their structure, stanozolol and danazol however not. Nevertheless, the side effects of this four AAS are comparable. Often the intake leads to nausea and vomiting as well as to a sore tongue, feeling to be stuffed and failure. Oxymetholone is also reported with a nausea, vomiting and diarrhea. These side effects appear very frequently by fluoxymesterone intake. However, the mechanisms of the side effects are not known in detail.

AAS are known in particular for their damage potential to the liver. The alkylation in the C-17 atom should endure the anabolic effectiveness during the first liver passage, indeed to the detriment of the liver tissue. In a survey nearly 30% of the interviewees know about these liver damaging effects of the AAS [12]. About 5% of the persons abusing high doses of AAS, like it is known for building up of muscles, declare liver problems but without a closer description [13].

There are many medical investigations about side effects of anabolic steroids on the liver available. The first sign of a liver damage is the increase of the concentration of the hepatocyte specific enzymes in the blood. The liver cell
damages can also lead to congestions of the small excretory ducts for bilious secretion, which can disturb the bilious outflow. Thus it can result in a more or less distinctive jaundice. If after longer-termed and strong abuse the abusers are forced to attend medical treatment because of acute illnesses, mostly further serious side effects appear.

By long-term overloading of the liver tissue it seems to come to development of carcinomas as late damage. Although the mechanisms of the origin of different cancer forms are not understood yet in all details, the epidemiological data show at least a clear connection. Different forms are described among them: hepatocellular adenoma, focal nodular hyperplasia and hepatocellular carcinoma [14]. Another dangerous late effect is the Peliosis hepatis, whose mechanism of origin is also not known yet. The Peliosis hepatis is usually poor in symptoms, so that their appearance is seldom noted. In a late stage it leads to life-menacing liver failure and in some cases it is ascertained only with an autopsy.

The liver tumors which appear in connection with the abuse of anabolic steroids are very strong vasculated, so that also here in a later stage, like the Peliosis hepatis, quite life-menacing bleeding can appear. In the end, deaths are also reported in particular from the circles of the bodybuilders with excessive medicinal supported building up of muscles. In these cases, the autopsies give other hints to the whole damage potential [15] in different organs.

Other anabolic substances

A chemical relationship between these so-called other anabolic working substances do not always exist. Their commonness is the anabolic side effect at least in higher concentrations. Clenbuterol and zilpaterol present the group of the beta-2 agonists, zeranol and tibolon the group of estrogen active substances. The anabolic trenbolon also belongs to the latter group. Some of the active substances originate from the animal mast, however, are approved only in few states beyond Europe. Clenbuterol, a beta-sympathomimetic, is a stimulant of the sympathetic nervous system and unfolds in larger quantities also an anabolic side effect. It has only one indirect influence on the gastrointestinal tract. Possible nausea and vomiting are probably of central-nervous origin. Zilpaterol has an effect like clenbuterol on the sympathetic nervous system and in this regard a high toxicity is discussed. However, the investigations limit themselves to toxicological considerations as remains in the animal food. Hence, there is no information available concerning the side effects in the digestive tract.
Tibolon is an estrogen- and progesterone-active steroid with low androgenic effect. Nausea is often described as a side effect after intake.

Zeranol is a toxin which is formed by molds of the type Fusaria. It works like a slight active estrogen. In some states it is permitted for mast of farm animals, but not in Europe. But zeranol is not permitted for human application. Hence, data about intake levels and side effects are not available. The substance is merely scientifically discussed in connection with long time toxicity and tolerable daily intake levels with the food.

S2. Hormones and related substances

The substance group of hormones itemized in the list of banned substances and methods is very heterogeneous concerning its effects on the organism. These substances which are mostly converted from preliminary stages in few metabolism steps to the active hormone intervene in different hormonal regulatory mechanisms. Because the effects are involved in very different regulatory mechanisms, the side effects of these substances have to be discussed individually.

Side effects of the growth hormone IGF-I (Increlex®) and somatorelin can be summarized in one group. IGF-1 supports the hGH effect, somatorelin releases hGH from the anterior pituitary gland. A brief application is generally free of side effects on the digestive tract, if some single reports after the market launch are neglected. Longer-term abuse of suprapharmacological doses leads to a general organ growth, thus also of the liver including functional disturbances. Epidemiological studies of the long-term therapy point to an increased risk of the development of a colorectal carcinoma [16]. The modes of action for this are not cleared up in detail.

Erythropoietin is considered as a well tolerated substance in general. Side effects on the digestive system are barely described. The appearance of nausea, vomiting and diarrhea usually appears on patients, treated with Erythropoietin as a therapy for their disease, before their treatment than under the treatment with Epoetin-alpha [17]. The disease itself seems to have stronger effects on the digestive system.

The application of insulin does not lead to side effects in the digestive system, neither with brief nor even with long-term therapy. However, it is discussed whether it is involved in the genesis of colon cancer.
Human choriongonadotropin is therapeutically used for women with insufficient oogenesis to fulfill the desire for children. In return it can stimulate the natural testosterone production of men. But most investigations were carried out on women. However, it can be supposed that the unspecific side effects like nausea and vomiting also occur with the substance abuse for testosterone stimulation in men.

Gonadorelin stimulates the formation of the luteotropic hormone. On a therapy with this releasing factor nausea and vomiting are frequently reported, additionally abdominal pain appears. Nevertheless, these side effects are not very intensive and quickly fade away.

The luteotropic hormone (LH) leads to a release of estrogen. Concerning the side effects in the gastrointestinal tract animal experiments showed that estrogen but not testosterone delays the stomach emptying [18] and raises the threshold of the pressure charm for the release of peristaltic movements [9]. Women under therapy often report unspecific nausea. The follicle-stimulating hormone (FSH) unfolds unspecific nausea, vomiting, feeling of fullness and diarrhea in the digestive tract. In rare cases FSH is also used for men and then frequently leads to an increase in weight.

**S3. Beta-2 agonists**

The beta-2 agonists have to be assigned to the group of stimulants. Their characteristic is the mostly selective and at least predominant effect on the beta-2 receptors in the sympathetic, adrenergic system. Especially these receptors can be numerous found in the bronchial tract.

The application of these agents is considered to be safe. Nevertheless, side effects in the digestive tract are to be expected, as the enterochromaffin cells of the small intestine liberate serotonin itself, due to the cholinergic effect of these cells. Furthermore, serotonin intervenes actively in the control of the gastric motility in the cholinergic system and on the other hand, raises the secretion of the mucosa cells. Like in other areas different receptor sub-groups were found for the serotonin, which are proved either in the same species in different areas of the ENS or in different forms in different species [19].

The side effects of beta-2 agonists can be explained by the generally known impact pattern of sympathetic activation. It has to be taken into account, that an inhalational application can anyhow affect the upper digestive tract up to the stomach due to the swallowing of considerable quantums of inhalants [20].
Occasionally, isoetharine leads to xerostomia, a typical sympathetic effect, and to taste disturbances (dysgeusia), like reported for formoterol or salmeterol. As an unspecific and rare allergic reaction irritation of the oral cavity and pharynx or the swell of the lips have to be assessed. In particular after inhalational application irritations in the oral and cervical cavity can appear. Such side effects are reported for formoterol, isoetharine and orciprenaline.

However, pyrosis, like it occurs with clenbuterol, terbutaline, tolbuterol or fenoterol, is a sympathetic effect of the stomach. As orciprenaline (Metaprotenerol) has not only beta-agonistic effects, nausea is a further frequent side effect. A study with more than 700 patients ingesting pirbuterol ascertained frequent side effects in the the gastrointestinal tract like nausea and vomiting [20].

S4. Substances with antiestrogenic effect

This group of agents can be divided into steroidal and non-steroidal aromatase blockers, selective estrogen receptor modulators and "blockers of the 3rd generation". Investigations to the appearance and frequencies of side effects of this substance group refer in the essentials to women with estrogen-sensitive tumors of the breast, which are treated with aromatase blockers. However, aromatase blockers are in particular also abused by men who abuse anabolics and want to prevent the metabolism of anabolic steroids in estrogen.

Anastrozol [21] and letrozol are non-steroidal aromatase blockers. In a phase I study with a non-steroidal aromatase blocker tested on healthy male volunteers a significant increase in LH and FSH blood concentration appeared and side effects like nausea, indisposition and dizziness [22] could be observed. However, results do not exclude that the nausea was caused by the dizziness. Another phase I study with letrozol [23] tested on postmenopausal women points out to the fact that no side effects on a significant level appear in this case. The same study using exemestane on postmenopausal women showed only few side effects, mainly in the gastrointestinal tract, like light gastritis, flatulence and diarrhea [24]. About the steroidal aromatase blockers like aminogluthedimide, exemestane, formestane and testolactone the loss of appetite, nausea also with vomiting and gastrointestinal discomfort are reported. Testolactone seems to have a high potential of releasing an unspecific allergic reaction, which process is not very severe.
Estrogen receptor modulators

The selective receptor modulators (SERM) [25] inhibit the estrogenic activity of the receptor so that the biochemical active cascade is missing. Nevertheless, estrogen remains in the bloodstream and can still release unspecific effects in the digestive tract.

The intake of tamoxifene leads to gastrointestinal disturbances, often expressed by nausea and vomiting. In a P-1 NSABP study [26] constipation was observed with a lower incidence. The similar agent toremifene [27] often releases nausea and vomiting, too. It is noteworthy, that clinical tests performed in the USA generally show a higher frequency of the prementioned side effects compared to European studies. The group of the other antiestrogen active substances are probably planned as "collecting ponds" for newer developments like tyrosine-kinase-inhibitors (Gefitinib®). Clomiphene [28], for instance, stimulates LH and is now and then accompanied by lower abdomen discomfort and flatulence and more seldom with nausea and vomiting. Cyclofenil releases in a case collection in 10 out of 30 women nausea and vomiting. The common choice criterion for those cases was a diagnosed impairment of liver function caused by a long-term intake of cyclofenil. The liver damages healed after discontinuing the medication [29]. Fulvestrant [30] releases very often nausea, vomiting, constipation or diarrhea and abdominal pain. Frequently, a loss of appetite appears, too. It has to be taken into account that all side effects can sporadically reach a severe level.

S5. Diuretics and other masking agents

Diuretics

The diuretics [30] are divided into different categories which induce forced urine excretion (diuresis) indeed, but with different mechanisms or acting at different places of the Nephrons. The loop-diuretics lead to rapid diuresis including electrolyte loss, in particular of potassium ions [31]. Therefore, potassium-saving diuretics were developed.

The benzothiadiazine derivatives work prior long lasting as well as the aldosterone antagonists, which are suitable for the long time therapy, whereas, the osmotic diuretics have a very narrow range of application.

The spectrum of side effects can be ascribed decisively on changes in the electrolyte balance. Thus, thiazides cause a sodium and calcium lack and loop-diuretics a potassium and calcium lack. The osmotic diuretics lead to a sodium
lack, too. Potassium-saving diuretics and aldosterone antagonists cause, like
the name expresses, a potassium profit. In summary, sodium, potassium and
calcium levels are the decisive factors which determine the side effect
spectrum. While sodium lack releases a strong thirst feeling, which disturbs
sensations of taste and can release cramps also in the upper abdomen, a
potassium lack leads to inertness of the intestinal musculature. Calcium lack
can also cause indigestion. Calcium has a pivotal function for the transfer of the
electrical impulses in the ENS.

The dryness of mouth via abuse of diuretics can be traced back to the reduced
reflexive salivary flow rate [32]. It is a fact, that the application of diuretics can
cause a thiamine deficiency, which excites symptoms in the nervous system
and can also lead to a loss of appetite [33]. Gastrointestinal discomfort like
diarrhea and constipation are apparently opposite symptoms. Nevertheless,
they can be explained by reduced water resorption out of the intestinal lumen
on the one hand and by the disturbance of the intestinal peristaltics caused by
the potassium loss on the other hand. The latter can also lead to abdominal
pain.

Thiazides lead to a temporary hyperglycemia [34]. The increased blood sugar
level inhibits the motility of the whole intestinal tract [35]. This explains at least
partially the gastrointestinal disturbances. Thiazides are also associated with
the appearance of cholecystitis. An epidemiological study about thiazide use
showed an increased relative risk of 2.4 compared with a control group
presenting a relative risk of 1.9 [36].

Generally, trouble and incidental bleeding of stomach indicates, just like
inflammatory processes and ulceration, to cell damages caused by the contact
with the drug. In this context, potassium salts play the essential role as they are
added to the diuretics for potassium substitution. Such inflammatory processes
can continue up to the small intestine.

Furosemide is first-pass metabolized to a very small proportion in the liver [37].
Animal experiments showed that the bioavailability of furosemide is strongly
raised by vitamin C [38], what has to be taken into account while application.
With etacrynic acid the gastrointestinal disturbances appear more frequently
and run severe, what is expressed through watery diarrhea and gastrointestinal
bleeding. The side effects of the potassium-sparing canrenone (Spironolactone)
contain often gastrointestinal disturbances like abdominal pain and diarrhea.
Epidemiological studies on the side effects of Spironolactone strongly allude to
the incidence of ulcers with stomach bleeding caused by the decreased healing
process of the mucous membrane, which is generally induced by aldosterone,
and in this case decreased by the antagonist [39]. Also the induction of cancer is supposed.

**Masking agents**

Probenecide is classed in the fight against doping as a masking agent. Its side effect spectrum on the digestive system is limited to the upper area. As general pathology nausea, feeling of fullness and also the loss of appetite can appear. It is also under suspicion to be liver-toxic and to cause necrosis. In clinical tests no appreciable side effects were ascertained for finasteride [40] and dutasteride [41].

The application of infusions is known to be applied to healthy but exhausted top athletes. In sports this act is attached very tightly to the therapeutic need. Any other intended application is evaluated as a prohibited method. However, infusion solutions can also develop side effects. The priority has to be given to the unspecific symptoms like nausea and vomiting, which can appear with the infusion of albumine- and dextrane-containing solutions. This can possibly be explained by the pressure change of the vascular wall of the precapillary arterioles, whose pressure receptors release transmitters that cause the enteral sensoric nausea. Hydroxyethyl starch (HES) infusions can lead to an enlargement of the salivary glands, whereas after application of albumine-containing infusions increased salivation can be released.

**S6. Stimulants**

The stimulants work as agonists directly on the alpha- and beta-receptors, which are on account of their different effects partitioned into these subgroups. Side effects of beta-2 agonists have been described in a former chapter.

The therapeutic application field for stimulants decreased during the last years. In particular as a central-nervously active appetite suppressant their application is judged very critically. Amphetamine and amphetamine derivatives belong ab initio the list of banned substances and methods to the group of stimulants and are known to have a high addiction potential. Amphetamines are indirect sympathomimetics and act as stimulants also on the liver and digestive tract, but indirectly by modulation of the ENS. However, especially one of the general injurious effects has to be followed in the context of sports, the deregulation of the body temperature at high physical exertion and thus the overheating of the body and its organs. In one study the following causes of death were
ascertained at 87 deaths by an involvement of amphetamines: overheating (34.5%), unknown causes (25.3%), accident (14.3%), hyponatremia (10.3%), heart-circulatory failure (9.2%), and liver failure (4.6%) [42].

Amphetamines and derivatives are metabolized by the cytochrome P450 oxydase system. This system is known for hereditary changes. This could probably be the reason why people react differently sensitive to this drug. Mostly, the affected persons are not in the knowledge of this idiosyncrasy. In this respect, the abuse of amphetamines and related substances can lead in worst case to acute liver failure. This results from the oxidative stress of the liver cells which causes the cell death. Light forms of hepatitis, mostly accompanied by jaundice and an increased bleeding inclination, are frequent [43]. The reason for this kind of jaundice is the disturbed removal of bile from the cystic ducts of the liver.

Preparations and active substances, which promise a selective fat combustion as for example Ma Huang, behave in a similar way. The extracts of this plant contain ephedrine and derivatives like Pseudoephedrine and also alkaloids in an extraction-dependent composition. Such preparations rescue the danger of direct liver cell damages as they contain liver-toxic materials and can strengthen and aggravate an existing, possibly not recognized liver pre-disease, respectively. In general the sympathomimetic symptoms are distinctive. The sympathetic innervation with direct effect on the stomach causes the side effects already described with the beta-mimetics. The enterochromaffin cells of the intestinal mucus membrane present adrenergic receptors. This allows the release of serotonin, which activates presynaptic the intestinal motility. In addition, the secretion into the intestinal lumen is increased. This sympathetic excitation results in an increase of the tonus of the sphincter ani and leads to a sluggish action of the bowels at the rectum sphincters.

Strychnine is no longer used for medication, as it really has a low therapeutic index and thus the application is problematic. It is toxic, tastes very bitter and causes reflectory oversecretion in the stomach [44] and vomiting [45].

S7. Narcotics

Central nervously acting analgesics of the morphine type belong to this closed group of active substances. The substances of this group have a high addiction potential. As mentioned before, their analgesic property is located central nervous, just like their side effects. But the side effects can also be of peripheral origin.
The frequent side effect of central nervous origin is nausea, often accompanied by unique or repeated vomiting. This is closely connected with the opiates working at the µ-receptor. The subjective perception of nausea is distinctive and also depending on the administered dose [46]. However, these symptoms occur significantly more often in women than in men [47]. The vomiting center is located in the brain stem between the extended spinal cord and interbrain, area postrema, Nucleus tractus solitarii and Formatio reticularis and is controlled by the neurotransmitters dopamine and serotonin.

It is also reported that morphine therapy can cause upper abdomen discomfort due to the fact that the general receptor linked tonicity-raising effect on the smooth musculature is transmitted as tension pain by the peripheral pain receptors [48]. This increased tonus affects also the sphincter between esophagus and stomach as well as the sphincter between stomach and duodenum. Tonus increase further leads to the reduction of the peristalsis, the directed aboral transport of the food mash. The inhibiting effect pertains the secretion of the salivary glands and the gastric juice secretion, too. Thereby, the food remains longer in the upper digestive tract and the lowering of the bowel peristalsis results in constipation of varying duration. This is supported by a strong dehydration of the faeces in the large intestine and spastic states of the sphincter ani.

In particular, µ-receptors were detected also in the presynaptic ganglia of the bowel. This is evidenced as the side effects in the bowel released by µ-agonists, e.g. constipation, are avoided by µ-antagonists that cannot pass the blood brain barrier. These antagonists do not affect the analgesic effect of the narcotics [49].

A retrospective study in a pain clinic about side effects of morphine on the digestive tract with patients less than 65 years old showed the following effects (sorted by frequency) [50]: Dry mouth (xerostomia), constipation, nausea, dysphagia, vomiting and diarrhea. Indeed, xerostomia is explicable by the anticholinergic effect of the narcotics. The precise mechanism itself is not cleared up to now. Probably, the authors describe the frequency of dry mouth too frequently, because dry mouth can have the most different causes. An evaluation of various scientific works about Pethidine set the appearance of side effects in relation to the concentration of the active substance in the plasma. At a blood concentration of already 0.15 mg/l dry mouth appeared; nausea occurred at a concentration above 0.25 mg/l [51]. A frequent loss of appetite is reported in this context with fentanyl, but cannot be assigned to this painkiller causally.
Animal experiments show that the liver is subjected to oxidative stress by morphine application [52]. This fact can probably be transferred to human liver cells. According to the spastic effect on the bile ducts in the liver and the contraction of the sphincter oddi biliary colics can also appear. Morphine inhibits the cholinergic stimulus transfer in animal experiments and thus the secretion of enzymes in the exocrine pancreas [53]. Spastic effects after morphine application can also be detected in the smooth muscle cells of the exocrine part of the pancreas and their excretory ducts. This contributes to the upper abdomen complaints.

S8. Cannabis

Cannabis has evolved into a party drug. According to different investigations approximately one quarter of the population between 15 and 58 years already tried cannabis once in their life. As frequent side effects on the digestive system nausea and vomiting are reported.

Today it is known that cannabis receptors (CB 1 and CB 2) are present in the digestive system, in particular in the area of the small intestine, whose stimulation unfolds a protective effect on the intestinal mucous membrane. Animal experiments show, that agonists of the CB 1 receptor located in the stomach lead also to a protective effect by lesions of the mucosa. On the other hand, this activation of CB 1 results in a worsening of pancreatitis induced by Coeruleine [54].

S9. Glucocorticosteroids

The glucocorticosteroids form a row of side effects and also some in the digestive tract [55]. The side effects mentioned here refer basically to the active substances Cortisone, Prednisone, Prednisolone and Dexamethasone.

Glucocorticosteroids are known for their anti-inflammatory effect. It is also a fact, that a systemic application regulates the metabolism into a catabolic state. This results in proteolysis and reduced cell proliferation. To what extent the intestinal mucosa and musculature are affected is not known yet, although intestinal disturbances are reported during the therapy. A development of ulcers in the stomach with long time therapy can be ascribed to the stimulation of the gastric acid secretion. Glucocorticoid receptors can be found in the large as well as in the small intestine. Especially in the small intestine they play a decisive role in the regulation of the electrolyte transport [56]. Due to the catabolic
metabolism effects a long-term overstraining of the liver and pancreas cannot be excluded, which comments then paradoxically in inflammatory processes. Furthermore, glucocorticosteroids lead to passing hyperglycemia, which inhibits in turn the intestine motility. This can also be expressed through health side effects in the digestive system.

**P2. Beta-blockers**

Therapeutically, beta-blockers prior serve the regulation of high blood pressure. As antagonists of the beta-sympathomimetics they control the opposite mechanisms of action in the ENS. Thus they block the secretion of serotonin in the enterochromaffin cells. Reduced secretion and a decrease in the tonicity of the smooth muscle cells of the intestinal wall are the result. Nevertheless, this has no influence on the passage of the chymus of a healthy person [57].

In the metabolism some substances of this material group work restraining on the fat oxidation [58] and lipolysis. For instance, this effect appears with Propanolole in healthy athletes during physical exercise [59]. Generally, beta-blockers decrease the liver blood flow what can possibly lead to light liver damages and Propanolole, in particular, decreases the enzymatic activity [60].

**D Summary**

Many mechanisms of the side effects of pharmaceuticals appearing in the digestive system are not understood yet, as the feedback control system of the ENS needs lots of additional scientific investigations. Side effects of doping related active substances on the digestive system are always given, however they are seldom severe or life-threatening. They fit into the general side effect spectrum, which is already summarized by Peters and coworkers [61].

In particular, polymedication, as it is known from the leisure and recreational sports [11], affects the digestive system by the appearance of not predictable side effects resulting from e.g. delayed or quickened resorption. Side effects in the liver also change the metabolism of the respective doping substance. To comment about possible late damages further investigations and epidemiological studies are essential.
References


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3.5 REPRODUCTIVE AND ENDOCRINE SYSTEM

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A Introduction

Many of the doping substances are hormones, their structural analogues, precursors of hormones or agonists/antagonists of their receptors. For this reason if used by healthy people they can cause endocrine imbalance and a number of other hazardous effects on the reproductive and endocrine systems. This review surveys the side effects caused by doping substances in athletes and healthy subjects but where is appropriate or data are unavailable studies on patients and animal studies have also been included.

B Anabolic Androgenic Steroids and Testosterone Prohormones

Androgens play a pivotal role in male reproductive and sexual function. They are required for the developing and maintaining masculine sexual characteristics – from the sexual differentiation in utero, through secondary sexual development during puberty to the establishment and the maintenance of adult sexual function and fertility. Testosterone, produced by the Leydig cells in the testes is the primary male sex hormone and is responsible for androgenic and anabolic effects observed during male adolescence and adulthood. Anabolic androgenic steroids (AAS) are synthetic derivatives of the testosterone and have similar biological effects [1]. Dehydroepiandrosterone (DHEA) and androstenedione are steroids in the sex hormone biosynthesis pathway and are precursors in the endogenous production of testosterone and estrogens. These steroid precursors are weak androgens secreted primarily by adrenal glands in both sexes. They provide a pool of circulating steroids that can be converted to active androgens and estrogens in the peripheral tissues. Adrenal androgens exert very little masculinizing and anabolic effects when secreted in normal amounts [2,3]. Testosterone, or its analogs, can act directly on target cells, or it can be converted to dihydrotestosterone (DHT) by the enzymes 5α-reductase or to estradiol by the enzyme aromatase in the peripheral tissues [1].

AAS are used in various sports for their anabolic (anticatabolic) effects to increase muscle mass, enhance athletic performance and physical appearance. Usually, these substances are used by athletes in dosages exceeding physiological replacement levels by 10 to 50 times or more [4]. This leads to hyperandrogenic conditions in the organism and results in anabolic steroid-
induced endocrine imbalance and impairment of the male and female reproductive functions.

**Anabolic androgenic steroids and male reproductive system**

The secretory and gametogenic functions of the testis are both dependent upon the secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, which stimulates the secretion of the anterior pituitary gonadotrophins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH helps maintain the spermatogenic epithelium by stimulating the Sertoli cells in the testes and LH stimulates the testosterone production by the Leydig cells. The production of testosterone provides the high local concentration of androgen to the Sertoli cells that is necessary for normal spermatogenesis. Although upon maturation the responsiveness for FSH of the Sertoli cells diminishes and switches to an increased responsiveness for androgens, a dual action of both FSH and intratesticular testosterone is necessary for complete quantitative and qualitative spermatogenesis [5].

As derivatives of testosterone, AAS have pronounced effects on the male hypothalamic-pituitary-gonadal axis and their use results in the clinical syndrome of hypogonadotrophic hypogonadism. This steroid-induced hypogonadal state is characterized by decreased serum concentrations of FSH and LH, low endogenous testosterone production, impaired spermatogenesis and testicular atrophy [6-8]. These effects stem from the negative feedback of anabolic steroids on the hypothalamic-pituitary axis and possibly from the local suppressive effects of excess androgens on the testes [6,9]. The administration of AAS mimics an enhanced level of circulating endogenous testosterone. High testosterone levels, as well as AAS, inhibit LH secretion by acting directly on the anterior pituitary and by inhibiting the secretion of GnRH from the hypothalamus. This in turn causes a corresponding decrease in secretion of both LH and FSH and the decrease in LH reduces the production of endogenous testosterone. Serum testosterone concentrations also decrease, except when exogenous testosterone is administered [5,10,11].

Administration of high doses testosterone induces supraphysiological levels of serum total and free testosterone. Serum concentrations of estradiol, androstenedione and DHT also increase because of peripheral conversion of AAS. In athletes on stacking regimen of androgens, plasma estradiol levels can rise as much as 7-fold to levels comparable to those normally seen in ovulating women. The AAS use reduces sex hormone-binding globulin (SHBG) levels [10-12].
High levels of testosterone are needed inside the testis for normal spermatogenesis and this can never be accomplished by oral or parenteral administration of AAS [5]. AAS use does not raise the androgen level in the testes to as great a degree, but inhibits LH and FSH secretion. Consequently, the net effect of AAS use is impaired spermatogenesis. With the impaired sperm production semen quality decreases, and infertility, manifested as oligospermia or azoospermia, along with abnormalities of sperm motility and morphology, often results. Due to these changes testicular atrophy (testicular shrinkage) is usually observed in male AAS users [7,8,13].

Recent animal studies have shown that high doses of AAS also reduce the length of seminiferous tubules [14] as well as suppress steroidogenic capacity (Fig. 1) and increase apoptotic tendency in Leydig cells (Fig. 2) [15,16]. These effects of AAS on the Leydig cells correspond to the suppression of serum testosterone concentrations after anabolic steroid use.

**Figure 1.** Activity of the key steroidogenic enzyme 3β hydroxysteroid dehydrogenase in Leydig cells (LC) of endurance trained rats treated with placebo (A) or nandrolone decanoate (B) x 200. The suppression is significant (P<0.001).

The anabolic steroid-induced state of hypogonadotrophic hypogonadism in male athletes is usually reversible after steroid withdrawal, but the time needed for full recovery of the hypothalamic-pituitary-gonadal axis and reproductive function is not exactly known [6]. After long-term AAS abuse spontaneous recovery may take up to 4-20 months [10,17]. Case reports indicate that problems may persist for up to 3 years and that recovery does not always occur [13,18]. Human chorionic gonadotrophin is sometimes used by athletes concurrently with anabolic steroids to prevent testicular atrophy or afterwards to promote quicker resumption of testosterone production by the testes. Data show that concomitant abuse of AAS and human chorionic gonadotrophin cause impairment on semen quality, although it seems that sperm count could be maintained with this regimen [19].
Gynaecomastia is another adverse effect observed as a result of AAS use [20]. Gynaecomastia is a benign enlargement of the male breast resulting from an altered estrogen-androgen balance. It is associated with the peripheral conversion of AAS to estrogens, due to the huge amounts of administered aromatizable androgens [6]. Rarely, a small amount of clear fluid is secreted [21]. A common practice among AAS users is to take aromatase inhibitors or selective estrogen receptor modulators such as tamoxifen to minimize side effects of estrogen and for the prevention of gynaecomastia. Once gynaecomastia is diagnosed cosmetic surgery is often needed to correct the problem.

Changes in libido appear to be a common adverse event reported by AAS abusers [20]. Although some data suggest that supraphysiological doses of exogenous testosterone do not increase sexual interest in healthy men [22], other studies have reported enhanced sexual desire, higher frequency of sexual behaviors as well as higher incidence of erectile difficulties in male athletes during AAS cycle in comparison with nonusers [21,23]. Reports indicate that towards the end of an androgen cycle some men may experience loss of libido probably related to the anabolic steroid-induced hypogonadism and low serum levels of androgens after cessation of AAS abuse [20]. Changes in libido do
Reproductive and Endocrine System

appear to normalize once baseline endogenous testosterone concentrations return [21].

In adult men, DHT mediates several effects of androgens including prostate hypertrophy and balding. Androgens play a permissive role in the development of prostate cancer and benign prostate hyperplasia and some data suggest that AAS use may increase prostatic disease risk [1]. AAS abuse can induce increased prostatic volume with decreased urinary flow rate [24] as well as adenocarcinoma of the prostate gland [25]. Androgenetic alopecia (male pattern hair loss) is accelerated in male AAS users who have inherited a tendency for baldness [21].

**Anabolic androgenic steroids and female reproductive system**

AAS have been associated with a number of adverse effects on female reproductive system, some of which are not reversible upon discontinuation of steroid use. Many of the differences in sexual characteristics between men and women are determined by testosterone. Therefore, it is not surprising that women who take AAS, too, gradually develop masculine secondary sex characteristics.

The secretory and gametogenic functions of the ovaries are both dependent upon the hypothalamic pulsatile secretion of GnRH, which stimulates the anterior pituitary to secrete gonadotrophins. FSH stimulates the early growth of ovarian follicles, and FSH and LH together are responsible for their final maturation and estrogen secretion from them. LH is responsible for ovulation, the formation of the corpus luteum, and secretion of estrogen and progesterone from the corpus luteum.

In the normal female body small amounts of testosterone are produced, and as in males, artificially increasing levels by administration of AAS will affect the hypothalamic-pituitary-gonadal axis. The increase in circulating androgens will suppress the hypothalamic-pituitary axis, resulting in a suppression of ovarian function, disturbances in menstrual cycle and infertility [1]. AAS administration decreases serum levels of LH, FSH, progesterone, and SHBG in women [26-28]. Female athletes using exogenous testosterone also have dramatically elevated serum testosterone levels [28,29].

Anabolic steroid use can result in inhibition of follicle growth and ovulation, and irregularities of menstrual cycle [21,27,30]. The observed menstrual abnormalities include dysmenorrhea, oligomenorrhea or amenorrhea [28,31]. Although these changes are generally more pronounced in younger women,
large inter-individual responsiveness to anabolic steroids exists. The effects are similar to the effects in patients treated with anabolic steroids. It is accepted that steroid-induced endocrine imbalance that results in disturbances of menstrual function and infertility is reversible [1].

The effects of AAS dosages, as generally used in sport on the hypothalamic-pituitary-gonadal axis in females are little studied [28]. Androgen-induced amenorrhea and more severe changes such as ovarian cyst formation (polycystic ovarian syndrome) with recurrent inflammation is reported as frequent damaging effects of AAS administration in female athletes from former East Germany [31]. Menopause also may be reached sooner in women who have a long history of anabolic steroid use [21]. In addition, animal studies show that high doses of AAS cause alterations in the uterus that are associated with a suppression of the reproductive capacity [32].

Other side effects of anabolic steroid use on female reproductive system are enlargement of the clitoris, decreased breast size and atrophy of the uterus [21,29,31]. Increased sexual desire is also reported in female AAS users. Changes in libido do appear to normalize after discontinuation of steroid use [21].

Additional masculinizing effects of AAS in women are lowering of the voice, hair loss and excessive hair growth on the face and body [21,31,33]. Virilization of the female’s voice is characterized by a lower fundamental frequency during speech, a loss of high frequencies and an increase in voice instability. These alterations can be explained by changes in the vocal cords as a result of AAS use [34]. The breast atrophy, hypertrophy of the clitoris, deepening of the voice, hirsutism and alopecia are generally irreversible.

Anabolic steroid use by pregnant women may lead to vaginal bleeding as well as to pseudohermaphroditism or to growth retardation of the female fetus [1]. Female pseudohermaphroditism is characterized by several grades of reproductive organs virilization of genetically female fetus as a result of excessive amount of circulating anabolic steroids during intrauterine life. The degree of prenatal masculinization is related to androgen concentration and to the embryonic development stage at the time of exposure. Other side effects in children born to mothers that have used AAS during pregnancy are skin challenge type of allergy, asthma-type problems with breath and damage of heart structures [31]. Animal studies show that prenatal testosterone propionate exposure reduces body weight of male and female offspring as well as induces dose-dependent malformations in reproductive organs and occurrence of prostatic tissue and seminal vesicles in females [35].
Anabolic androgenic steroids and reproductive system of children and adolescents

Anabolic steroids administered to growing children and adolescent athletes cause more side effects than they do in adults both qualitatively and quantitatively [31]. In pre- and peripubertal children side effects include development of pubic hair, clitoral/phallic enlargement and other signs of virilization or precocious puberty [3,36]. Gynaecomastia is more pronounced in children who are given androgens, possibly due to a greater capacity for extraglandular aromatization [1]. The side effects of AAS use are generally more pronounced in adolescent girls than in women and the atrophy of the uterus is a typical side effect in girls. Reduction of female breast and amenorrhea are common. The decision to undergo a sex transformation taken by a former East German female athlete suggests that long lasting AAS intake during puberty could lead to sexual identity disturbances in women [31].

Other endocrine effects of anabolic androgenic steroids

AAS abuse could lead to impairment of thyroid function in male and female athletes. In male athletes, administration of AAS has been found to decrease serum concentrations of the iodine-containing hormones secreted by the thyroid gland – triiodothyronine (T₃) and thyroxine (T₄). Thyroid binding globulin (TBG) is also reduced [11,37,38]. The reports of serum thyroid stimulating hormone (TSH) changes found after AAS administration are controversial. Increased serum TSH after short-term AAS treatment [38] and reduction or no differences in TSH levels after a prolonged AAS use have been observed [11,37]. The TSH response of pituitary after thyrotrophin-releasing hormone stimulation is increased in male bodybuilders using high doses of AAS [37]. In female weight lifters administration of AAS decreases serum concentrations of T₄ and thyroid binding proteins, and increases the TSH levels [28]. The mechanisms of these effects of anabolic steroids on the thyroid function are still not entirely clear. The changes reverse within weeks after discontinuation of AAS use [11].

Anabolic steroid use may induce insulin resistance and diminished glucose tolerance. These changes mimic type 2 diabetes and are observed in patients treated with 17-alkylated oral androgens [1] and in male athletes using AAS over a long period of time (3-7 years) [39]. Although there has been no documented diabetes mellitus in athletes using anabolic steroids, these changes are associated with increased cardiovascular risk.
AAS abuse can decrease serum corticotrophin (adrenocorticotropic hormone, ACTH) concentrations. An initial and transient decrease in cortisol is also observed. The suppression of ACTH is reversible after steroid withdrawal [10]. Recent data suggest that long lasting AAS abuse may enhance tissue activity of the renin-angiotensin-aldosterone system in bodybuilders, which can also increase the risk of cardiovascular disease in athletes [40].

**Side effects of testosterone precursors**

DHEA, androstenedione and androstenediol are produced by adrenal, gonadal and peripheral steroidogenic pathways as part of the normal sexual and reproductive hormonal milieu in both genders. Athletes use DHEA and various forms of androstenedione and androstenediol as testosterone prohormones in an attempt to elevate testosterone levels. Research indicates that the use of prohormones supplements does not produce either anabolic or ergogenic effects in healthy men but can lead to endocrine imbalance and other side effects similar to those induced by synthetic AAS [2,3].

DHEA administration increases serum DHEA and androstenedione concentrations in men. Serum estradiol is also elevated in older men [2]. Prolonged androstenedione and androstenediol intake in men does not uniformly increase serum testosterone, but increases serum androstenedione, DHT and estrogen (estrone and estradiol) concentrations [3]. The characteristics of the enzymes involved in the interconversion of androstenedione suggest that, although larger doses of androstenedione may increase serum testosterone concentrations, still larger increases would occur in serum estrogens and DHT. The data about the effect of androstenedione on serum testosterone levels in men are controversial – the effect seems to depend on the dose, the age and the basal serum testosterone concentrations. In healthy men a moderate and transient increase of serum testosterone concentrations can be seen only after high doses (200-300 mg) of androstenedione, but no differences with controls can be found after long-term use [2,41]. Some data suggest that prolonged (12 weeks, 200 mg•d-1) androstenedione use may downregulate endogenous testosterone production by lower serum LH levels [41]. Undoubtedly, many users consume daily doses substantially higher than those used in these studies and for a longer time period [3]. Case reports indicate that in young male bodybuilders long lasting (1 year) androstenedione use can cause priapism [42] as well as suppression of the hypothalamic-pituitary-gonadal axis resulting in very low serum total and free testosterone levels, severe oligospermia, testicular atrophy and loss of
libido [43]. The long-term health effects of prohormones supplementation are unknown. The altered hormonal milieu caused by prohormones intake (elevated serum androstenedione, DHT and estradiol concentrations) is similar to the hormonal profile observed in men with gynaecomastia, prostate cancer, testicular cancer and pancreatic cancer [2]. In addition, animal studies have found resultant hyperplastic prostatic changes with androstenedione use [44].

There are no data available on the effects of DHEA administration in young women. In older women chronic intake of DHEA increases serum DHEA, androstenedione, testosterone, DHT and estrogen levels, decreases serum LH and FSH concentrations and causes adverse virilizing effects, impaired insulin sensitivity and glucose tolerance [2,3,45]. Androstenedione intake in women causes a large increase in serum androstenedione and testosterone concentrations. In women, 50-100 mg of androstenedione intake does not change serum estradiol, but a significant, acute increase is seen in estradiol levels after intake of 300 mg [2,3]. Although there are no available data on the effects of prolonged androstenedione or androstenediol administration in women, the change in the hormonal milieu resulting from prohormones use may cause masculinizing effects along with other negative effects similar to those observed after DHEA and AAS use.

C Growth Hormone and Insulin-like growth factor-1

Growth hormone (GH) is a peptide hormone secreted by the anterior pituitary. GH’s major action is to stimulate protein synthesis. GH also mobilizes fat by direct lipolytic action and has a hyperglycemic effect. GH stimulates the synthesis of insulin-like growth factor I (IGF-I) in all tissue. In most tissues IGF-1 has local actions, but liver secretes it into the circulation. IGF-1 also stimulates protein synthesis, but it has a weaker lipolytic action and hypoglycemic effect [46,47]. The long-term risks of high doses GH use in athletes are not well known. Patients who have acromegaly with chronic endogenous GH excess (consequence of somatotroph pituitary adenoma) may be the most accurate model for an athlete who supplements an already normal hormone level.

Growth hormone and reproductive system

The impairment of gonadal function is a common clinical finding of acromegaly in both sexes, but its pathogenesis remains unclear. Recent data suggest that not only FSH/LH deficiency (caused by the tumor mass effect) and/or
hyperprolactinemia, but also GH excess per se could be responsible for these effects in at least some of these patients [48].

Menstrual irregularity (amenorrhea, oligomenorrhea, polymenorrhea) is common in women with acromegaly in reproductive age. Compared to patients with normal cycles, patients with menstrual abnormalities are more hirsute, have lower serum estradiol and SHBG concentrations, but similar testosterone levels. Gonadotrophin deficiency with or without concomitant hyperprolactinemia appears to be the major cause of the menstrual irregularity in women with amenorrhea and larger tumors. However, some women with oligomenorrhea and also those with regular cycles show many of the clinical and biochemical characteristics of polycystic ovarian syndrome. Recent data suggest that elevated GH levels per se are responsible for the high prevalence of signs of hyperandrogenism in women with chronic GH excess, either directly or via the effects of the induced hyperinsulinemia leading to reduced SHBG levels. This, in turn, may lead to menstrual abnormalities [48].

Most men with acromegaly have hypogonadism associated with a reduced sperm number and considerably reduced sperm motility. Serum FSH, testosterone and DHT concentrations are lower, whereas estradiol levels are higher in acromegalic patients than in controls [49]. The mechanisms of these effects are not well understood but the data of an animal study has shown that administration of very high doses of GH induces reduction of testes and prostate weights, germ cells degenerations, and notable reduction of LH and testosterone levels [50]. At partial variance with these experimental findings in dogs, men with chronic GH excess have prostate enlargement with a high prevalence of prostate abnormalities [51].

Other endocrine effects of growth hormone

It is well established that GH counteracts the effects of insulin on glucose and lipid metabolism, although it shares anabolic properties on protein metabolism with insulin. GH is a diabetogenic hormone and the anti-insulin or counterregulatory effect of GH is characterized by decreased glucose uptake into skeletal muscles, increased hepatic glucose production, rising blood glucose levels and increased insulin secretion. There is increasing evidence that this effect may occur secondary to the lipolytic effect of GH. Exposure to supraphysiological doses of growth hormone in the pathophysiological model of acromegaly leads to insulin resistance, impaired glucose tolerance, and clinically overt diabetes mellitus [51]. Similar effects have been observed in healthy men after GH administration. High doses of GH increase fasting insulin
and insulin resistance in endurance trained athletes [52] and glucose intolerance or diabetes develop significantly more often in healthy aged men after GH treatment than in controls [53].

GH use could lead to impairment of thyroid function. GH administration stimulates extrathyroidal conversion of T₄ to T₃ in a dose-dependent manner and suppresses circadian TSH levels in GH-deficient adults [54]. Administration of high doses GH to endurance trained athletes increase free T3 into supraphysiological range and reduce free T4 [52]. The long term effect of high doses GH use on thyroid function in athletes is unclear, but GH and IGF-1 excess cause thyroid overgrowth, which is a common phenomenon in acromegaly. Chronic GH excess is frequently associated with the presence of nodular or diffuse goiter [51].

Other consequences of chronic GH excess are hyperparathyroidism and increased risk of neoplastic complications [51]. Several lines of evidence show a relationship between the GH/IGF-1 system and cancer development. IGF-1 could increase epithelial cell proliferations and prevent apoptosis. GH administration increase serum IGF-1 concentrations [53] and epidemiological studies show that high-normal IGF-1 levels in healthy adult subjects may be associated with an increased risk of breast, prostatic and colorectal cancer. In addition, the mortality from cancer-related complications is increased in acromegalic patients [51].

**D Gonadotrophins**

LH is secreted by the pituitary gland. It stimulates ovulation and luteinization of ovarian follicles in women and the testosterone production by the Leydig cells in men. Human chorionic gonadotrophin (hCG) is secreted during pregnancy and stimulates testosterone secretion by the fetal testis. hCG has almost the same effects on the reproductive system as LH. hCG is used by athletes to increase the endogenous testosterone production. Administration of hCG may result in ovarian hyperstimulation syndrome in women [55] and may induce gynaecomastia in men [13]. The concomitant abuse of hCG and AAS causes impairment to semen quality in male athletes. A significant positive correlation has been found between the hCG dose during the AAS cycle and the relative amount of morphologically abnormal spermatozoa [19].
E Insulin

Insulin is secreted by the beta cells of the islets of Langerhans in the pancreas. Insulin stimulates lipogenesis and has an inhibitory effect on lipolysis, proteolysis, glycolysis, gluconeogenesis and ketogenesis. Insulin stimulates the translocation of glucose transporters from the cytoplasm of muscle and adipose tissue to the cell membrane and increases the rate of glucose uptake. Insulin thus lowers blood glucose concentrations through inhibiting hepatic glucose production and through accelerating glucose uptake [46].

Abuse of insulin by athletes as performance-enhancing agent may result in hypoglycemia and hypoglycemic coma [56]. The risk of hypoglycemic coma is increased in overdosing and using insulin during increased physical activity and/or inadequate diet. Physical exercise increases the insulin sensitivity of the skeletal muscles by causing an insulin-independent increase in the number of the glucose transporters in cell membranes. Exercise can precipitate hypoglycemia not only because of the increase in glucose uptake but also because absorption of injected insulin is more rapid during exercise. The symptoms of hypoglycemia include sweating, anxiety, hunger, tremor, cognitive abnormalities, convulsions, lethargy, etc. Unless treated promptly hyperglycemia may result in coma and death.

F ACTH and Glucocorticosteroids

Glucocorticosteroids are steroid hormones secreted by the adrenal cortex. Glucocorticosteroids have catabolic, lipolytic and hyperglycemic effects. They are essential for the response to stress. Under the effects of various stressors hypothalamus secretes corticotrophin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete ACTH. ACTH increases the synthesis and the release of glucocorticosteroids (and adrenal androgens) from the adrenal gland. In clinical practice glucocorticosteroids are used mainly for their anti-inflammatory and immunosuppressive effects. The long-term use of glucocorticosteroids is associated with serious and sometimes irreversible side effects [57].

Glucocorticosteroids and reproductive system

Administration of glucocorticosteroids reduces testosterone levels in men [58]. Data from animal studies suggest that one of the possible mechanisms of this effect is impairment of LH signal transduction and steroidogenesis in the Leydig
cells [59]. Estrogen is reduced in women after glucocorticosteroid treatment and menstrual irregularities and amenorrhea can occur. Delayed puberty can also be observed. Corticosteroid use during pregnancy may cause intrauterine growth retardation and adrenal suppression in the baby [58].

Other endocrine effects of glucocorticosteroids

Typically, the side effects of long-term glucocorticosteroid administration on the endocrine system include iatrogenic Cushing’s syndrome, diabetes mellitus, adrenal atrophy and growth retardation [57]. The Cushing’s syndrome is characterized by a moon face, buffalo hump, central obesity, glucose intolerance, osteoporosis, etc. The reason for the cushingoid habitus is not clearly understood but one hypothesis is that truncal and peripheral adipocytes vary in sensitivity to the glucocorticosteroid facilitated lipolytic effect [57,58]. Glucocorticosteroids elevate blood glucose and produce a diabetic type of glucose tolerance curve. The major diabetogenic effect of glucocorticosteroids is an increase in protein catabolism with increased gluconeogenesis. Glucocorticosteroid excess causes decreased glucose tolerance and insulin resistance and one fifth of patients may develop overt diabetes. Upon discontinuation of the steroids, the diabetes normally disappears [57,58]. Glucocorticosteroid administration suppresses hypothalamic-pituitary-adrenal axis. Glucocorticosteroids inhibit ACTH secretion by acting directly on the anterior pituitary and by inhibiting the secretion of CRH from the hypothalamus. The suppression of ACTH levels leads to atrophy of the adrenal cortex and secondary adrenal insufficiency with low serum cortisol concentrations. This adrenal insufficiency becomes clinically relevant if exogenous therapy is withdrawn too rapidly (hypotonia) or in the case of stressful situations when higher glucocorticosteroid levels may be required. The frequent use of glucocorticosteroids by athletes necessitates testing for adrenal insufficiency because of the risk of death in cases of associated severe stress (trauma, infection, surgery) [60]. In addition, it is not only the synthesis of endogenous glucocorticosteroids that is depressed but also the synthesis of the adrenal androgens. In females, this way may lead to nullification of androgen-dependent anabolism, e.g. of the bones [57]. Glucocorticosteroids can inhibit linear growth. The mechanism is unknown but may involve a combination of reduced GH production and a direct inhibitory effect on bone and connective tissue. Growth failure is commonly experienced by children receiving prolong glucocorticosteroid therapy [58].
Endocrine effects of ACTH

ACTH increases the secretion of glucocorticosteroids and adrenal androgens from the adrenal cortex. The artificially increasing levels of ACTH caused by ACTH misuse in healthy subjects may mimic excess hormone secretion observed in patients with some pituitary tumors resulting in ACTH-dependent Cushing’s syndrome (Cushing’s disease). Besides the other signs of the Cushing’s syndrome, the level of the weak mineralcorticoid deoxycorticosterone may be elevated by ACTH leading to salt and water retention. The secretion of adrenal androgens will be also elevated and may result in masculinizing effects (hirsutism, acne) in women.

G Stimulants

Central nervous system stimulants, such as amphetamines and cocaine, may be used by athletes to reduce tiredness and increase alertness, competitiveness, and aggression. They are more likely to be used in competition but may be also used during training to increase the intensity of the training session [61]. Amphetamines and cocaine are powerful addictive stimulants; they have high potential for abuse and produce intense physiological and psychological side effects including also effects on the reproductive system. Amphetamine use during pregnancy is associated with increased risk of maternal, fetal and infant death, fetal growth restriction and birth defects [62, 63]. Causes of maternal deaths include intracerebral hemorrhage, cardiovascular collapse and amniotic fluid embolism [63]. Cocaine administration decreases serum estradiol concentration and disrupts menstrual cyclicity and folliculogenesis in female animals [64]. Cocaine use during pregnancy can cause spontaneous abortion, placental abruption, fetal growth restriction, preterm labour, low birth weight and variety of congenital malformations (cardiac abnormalities, genito-urinary and gastro-intestinal tract defects) [62,65]. Some data suggest that fetal malformations related to maternal cocaine administration are the result of vasoactive effects of cocaine leading to hemorrhage, oedema and hypoxia [70]. In men, chronic cocaine use is associated with loss of libido [61] and increased risk of priapism [66].

H Narcotics

Narcotics are naturally occurring or synthetic drugs which bind to opioid receptors to produce physiological effects. In medical practice narcotics are used in the management of severe acute pain and moderate or severe chronic
pain. Long term administration of narcotics may result in endocrine side effects as opioid receptors (and endogenous opiates) are involved in the regulation of some hormones. In humans, the acute administration of opioids in healthy men increase prolactin, GH, TSH and ACTH secretion but inhibits LH release [67]. Chronic intrathecal administration of opioids has been found to induce central hypocorticism in 15%, GH deficiency in 15% and hypogonadotrophic hypogonadism in almost all patients. Decreased LH, estradiol and progesterone levels, menstrual irregularities including amenorrhea and decreased libido are observed in women receiving intrathecal opioids [68]. It appears that the impact of opioids on testosterone production depends on the route of administration. Significantly lower testosterone and LH levels are observed after intrathecal administration [68] but modest or no changes in testosterone have been reported in heroin addicts [69]. However, decreased libido and impairment of spermatogenesis have been observed in men receiving intrathecal opioids as well as in heroin addicts [68,69].

I Cannabinoids

Cannabinoids are isolated from Cannabis sativa and Cannabis indica plants. Of the natural phytocannabinoids, tetrahydrocannabinol (THC) is the main source of the effects caused by the consumption of cannabis [70]. Cannabinoids exert their effects through the activation of two specific receptors located on the surface of the target cells. Recent evidence suggests that multiple endocannabinoid ligands may also play an important role in the maintenance and regulation of early pregnancy and fertility. Furthermore, endocannabinoids are involved in the anterior pituitary and hypothalamic control of sex hormones [71]. Marijuana, THC, and other exogenous cannabinoids exert potent effects on this homeostasis. Thus, they have the potential to produce pronounced adverse effects on male and female reproductive systems [72].

**Cannabinoids and male reproductive system**

In males, cannabis smoking decreases serum LH concentrations. In some studies chronic marijuana use has been shown to be associated with decreased plasma testosterone levels, but other studies have failed to reproduce these findings. Reduced sperm counts in males have been more consistently seen. Animal studies indicate that acute and chronic THC exposure decreases testicular weight and depresses testosterone synthesis probably by reducing
gonadotrophin levels. High doses of THC causes an increase in abnormally formed sperm in rodents [72].

**Cannabinoids and female reproductive system**

In women, acute administration of THC suppresses the secretion of LH in the luteal phase. In chronic users, it shortens the menstrual cycle, the effect being predominately a short luteal phase leading to menstrual irregularities and anovulation [71]. Animal studies show that THC produces dose-related inhibition of pulsatile LH release and preovulatory LH surge. Some data suggest that the decreased release of hypothalamic GnRH into the pituitary is responsible for the suppressed level of LH. The possible mechanism of this effect of THC is modulation of neuronal systems known to inhibit GnRH secretion. Cannabinoids have also an inhibitory effect on prolactin release in female animals [71,72].

Several experimental and clinical studies have shown adverse effects of marijuana exposure on embryo development and in early pregnancy. In women cannabis use during pregnancy is correlated with low birth weight, prematurity, intrauterine growth retardation, presence of congenital abnormalities, perinatal death and delayed time to commencement of respiration [72,73,62]. THC exert a potent direct relaxant effect on human pregnant myometrium and these findings rise the possibility that regular use after term might delay the onset of labor and therefore increase stillbirth rates, as shown in animal studies [74]. THC exposure results in increased miscarriage, fetal deaths, stillbirths and neonatal deaths in animals [73]. It is reported that THC-exposed male mouse fetuses have significantly reduced testosterone concentrations and testis weight [72].

**J Beta–Blockers**

Beta-blockers block the action of catecholamines on β-adrenergic receptors. Their chronic use in clinical practice is associated with detrimental effects on insulin sensitivity, glycaemic control and the incidence of type 2 diabetes mellitus. Research has shown that most beta-blockers significantly decrease insulin sensitivity and increase the risk for development of new-onset diabetes. The mechanisms of this effect are not fully understood, but several possibilities have been put forward: body weight gain, decrease in insulin secretion, and probably most important, reduced blood flow to muscles and subsequent reduced insulin-stimulated glucose uptake [75]. Recent data suggests that beta-
blockers induce a worsening of sexual activity and a reduction of plasma testosterone concentrations in male hypertensive patients [76].

K Conclusion

These data clearly suggest that most doping substances disrupt the hormonal balance of human body exerting serious side effects on the endocrine and/or male and female reproductive systems. Some of these effects persist long after the substances have been discontinued and may become irreversible. Their severity depends on the gender and age of user, the specific substance and dosage used, and the duration of intake. The bodies of adolescent girls and boys are especially susceptible to the side effects described above. Many athletes use several doping substances either simultaneously or in various regimens, in which case the harm done to the body can be severer and the consequences quite unpredictable. In some cases the artificially induced hormone imbalance may increase the risk of development of neoplastic conditions and/or is potentially lethal.

L References


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3.6 RENAL DISORDERS AND ELECTROLYTE METABOLISM

Nikolaos Koutlianos, Evangelia Kouidi

A Introduction

The abuse of banned substances and/or methods in sports for the enhancement of physical performance may cause numerous health disorders. One should keep in mind that firstly all drugs have side effects, secondly too large a dose increases the risk of undesirable effects and thirdly the effect of some drugs can be altered markedly by the administration of other substances - agents. Athletes using excessive amounts of drugs have an increase likelihood of impaired renal excretion of drugs and nephrotoxicity, since the drugs are excreted from the kidneys. Although rare, adverse renal effects have been reported, leading mostly to renal failure or even Wilms’ tumors in isolated cases (especially in body-builders using anabolic steroids) [1]. The major renal, urinary and electrolyte side effects of prohibited substances abuse in sports are presented in table 1.

Table 1. Possible adverse renal effects and electrolytic disorders of banned drugs abuse.

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<td>Hyperkalaemia</td>
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<td>Elevated creatinine</td>
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<td>Renal overfunction</td>
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The functions of the kidney can be divided into two major groups: secretion of hormones and extracellular homeostasis. The kidney preserves the extracellular homeostasis by maintaining a balance in several substances such as: water, glucose, amino acids, urea, bicarbonate, protons, sodium, chloride, potassium, calcium, magnesium and phosphate. Furthermore, the renal function is responsible for retaining a stable balance of sodium and water in the body. The major homeostatic control point for maintaining this equilibrium is renal excretion. Abnormal ranges of the fractional excretion of sodium can imply acute tubular necrosis or glomerular dysfunction [2].

B Renal Side Effects

Androgenic-anabolic steroids (AAS) are the most popular drugs among athletes, but their chronic abuse is associated with a lot of side effects in almost all systems, as reproductive, cardiovascular, endocrine etc. [3]. Zeier et al. reported that the magnitude of renal risks in adults depend on gender and may be presumably mediated via sex hormones [4]. Testosterone renal receptors probably play a crucial role and they may set the stage for accelerated progression of renal disease in the athlete exposed to male sex hormones.

The accelerating effect of high protein consumption in the process of chronic renal failure has been well known for many years. Bodybuilders usually prefer a high-protein and creatine-supplemented diet in order to achieve maximal morphological adaptations in skeletal muscles. Weightlifters often experience a rise in serum creatinine as a result of increased skeletal muscle mass. On the other hand, AAS use may elevate serum creatinine levels, blood urine nitrogen and uric acid. These values often return to normal once the drugs are discontinued [5, 6]. The combination of AAS and creatine supplement that has been currently abused by body builders may also cause severe renal damage. Revai et al. reported a case of severe nephrotic syndrome with diffuse membranoproliferative glomerulonephritis in an athlete using AAs and creatine for a long time [7].

Wilm’s tumor, uncommon in adults has been reported in several athletes using AAS [8]. There is evidence suggesting that steroids are weak carcinogens that can initiate tumor growth or promote such growth in the presence of other carcinogens [9, 10]. It is suggested that the long-term use of AAS should be at least considered as etiologic factor for renal cell carcinoma occurrence [11, 12].

There are only a few studies indicating a potential linkage between the use of AAS and acute renal failure (ARF). Abuse of stanozolol was found to cause
severe cholestasis and ARF [13]. The renal biopsy findings were consistent with resolving acute tubular necrosis white light or electron microscopy revealed no glomerular changes. ARF as a complication of rhabdomyolysis in a body builder using AAS has also been reported [14]. Furthermore, attention should also be paid to the possibility of interstitial nephritis as an adverse effect of AAS abuse.

Chronic hypovolaemia, which is frequently found among athletes using AAS, may magnify renal damage processes or electrolytic disorders. These side effects are often exacerbated by diuretics as well.

Renal failure due to even intermittent consumption of increased doses of beta-adrenergic substances and/or AAS should be recognized in general. Hartung et al. studied a 27-year-old male body-builder referred for azotaemia who had regularly taken testosterone as well as clenbuterol tablets for 18 months [15]. The combined use of clenbuterol and AAS seems to increase the risk of renal failure especially in pre-existing kidney diseases. The renal biopsy revealed nephrosclerosis with pronounced obstructive lesions of preglomerular vessels, hypertension-like vascular damage, global glomerulosclerosis and diffuse chronic tubulo-interstitial damage. Beta-adrenergic substances may lead to acceleration of a hypertensive renal damage process. High to toxic doses of clenbuterol are found to cause a remarkable beta-adrenergic receptor down-regulation in rats [16]. An additional adverse effect of clenbuterol may be interstitial nephritis and hypertensive nephrosclerosis [15].

Diuretics have the ability to increase urine production and secretion and are frequently used by athletes either to excrete the banned drug or to lose weight rapidly [17]. However, urinary tract fluid losses caused by drug-induced diuresis may lead to intravascular volume depletion sufficient to cause ARF. Excessive diuretic therapy in combination with increased ephidrosis, usually lead to dehydration and hypovolemia, which is one of the major causes of hypokalaemia [18].

Athletes using ephedrine are at increased risk of rhabdomyolysis [19]. Rhabdomyolysis and myoglobinuric ARF may occur with cocaine overdose, alcoholism and excessive exercise, while ARF due to hemolysis is also seen following blood transfusion reactions. Moreover, alcohol is a diuretic and contributes to a state of dehydration. Therefore, attention should be paid particularly by athletes performing in the heat.

Nutritional supplements such as cobalt may be frequently abused in sports. Cobalt is an element which presents properties similar to those of iron and nickel, leading to a significant and stable polycythemic response through a more efficient transcription of the erythropoietin gene [20]. However, renal adverse
side effects may be produced by cobalt salts administration since cobalt accumulates especially in kidney, promoting organ damage and renal dysfunction due to enhanced oxidative stress, even at low dosage below of 34 mg/kg [21].

C Electrolyte Metabolism Disorders

Doping-triggered disorders in electrolyte homeostasis are concomitantly linked to renal function. It is well known that kidneys regulate the amount of water, sodium, potassium and other electrolytes in the body. Diuretics are justifiably considered as the major category of banned drugs in sports, which is mostly linked to disturbed electrolyte metabolism.

Unlike medical patients, athletes do not retain excess water, thus the use of diuretics results in an abnormal and dangerous loss of water and electrolytes. Athletes with diuretic-induced dehydration, performing in heat, are more susceptible to heat exhaustion. Hypotension can be particularly troublesome sometimes. Use of diuretics commonly leads to low levels of body potassium. However, severe symptomatic hypokalaemia is rare, while moderate levels of hypokalaemia are common [18]. Hypokalaemia mainly causes disturbed neurological functioning and cardiac arrhythmias, even heart failure. Additionally, symptoms as muscle weakness and muscle cramps are common.

On the other hand, overuse of diuretics such as spironolactone, triamterene and amiloride may lead to extremely high potassium concentration in the blood. Hyperkalaemia may lead to malignant arrhythmias. Appleby et al. reported a case of a 31-year-old body-builder with serum potassium 6.7 mmol/l, which caused a run of sustained ventricular tachycardia [22]. Furthermore, most diuretics disturb the metabolism of uric acid and this can precipitate a painful attack of gout. Nevertheless, anabolic agents also influence electrolyte concentrations. AAS use may lead to increased levels of potassium, sodium, calcium and phosphate, which can ultimately result in atrial and ventricular fibrillation [23].

Oral or parenteral abuse of glucocorticoids may also lead to electrolyte disorders. Widmer et al., reported that the administration of prednisone (5 to 2000 mg/d) was a significant risk factor for hypokalaemic events in various patients [24]. However, these findings are not yet confirmed in athletes abusing glucocorticoids for doping.

Additionally, sodium’s levels are frequently found increased in athletes mainly due to supplements’ abuse. Indeed, numerous athletes intake sodium
bicarbonate or sodium citrate in an attempt to enhance their athletic performance, especially, in activities of high intensity and involving large muscular groups (e.g. 400 m running). However, elevated sodium levels may lead to gastrointestinal disturbances and they are often accompanied by diarrhea especially for sodium bicarbonate supplement [25].

D Conclusion

Banned substances users should be aware that many of the adverse effects might be present without obvious warning signs. This statement seems to be valid also for renal side effects. AAS and diuretics abuse, often combined with high-protein diet can result in severe renal failure and electrolyte imbalance-triggered side effects such as malignant arrhythmias. Much of our knowledge about these potentially severe but usually limited side effects is confounded by the concomitant use of various substances. With the knowledge about the effects and side effects physicians should adequately counsel and educate athletes, parents and coaches to avoid doping.

E References

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3.7 IMMUNE SYSTEM AND SKIN: THE IMPORTANCE OF STUDYING THIS PROBLEM

Eduardo Ortega, Mª Dolores Hinchado, Esther Giraldo

Today there is still a big lack of information about the scientific knowledge of the side effects of doping in both competitive sports and recreational ones. In addition this knowledge is not always unified, and it is very important to harmonise in Europe the scientific information about the biomedical side effects of doping, in order to get chance for preventing this practise.

Most of the information about the side effects of the different doping substances is available on the respiratory and cardiovascular systems as well as the brain. However, little information is currently examined about the side effects of doping substances on the immune system. Today, it is clearly known that exercise modulates the immune system, and while moderate exercise stimulates most of the immune responses, intense exercise can be dangerous for the adaptative response mechanisms. In addition, the exercise-induced changes are mediated by different hormones released during the exercise, mainly the so called “stress hormones”. Then, a modification of the neuroendocrine balance by hormones intake during exercise practise modify the feed-back of neuroimmune mechanisms, and may seriously affect the normal function of the immune system, damaging sportspeople’s health.

However, although there are a lot of investigations about different substances (i.e. anabolic steroids, stimulants, narcotics, diuretics, nutritional supplements…) related to doping, and about these substances on immune system at pharmacological concentration; nothing is known about the biomedical side effects of these doping substances (at raised blood concentrations) on the immune system during exercise, an special physiological situation.

The purpose of this communication is to emphasize the importance of studying the biomedical side effects of doping substances on the immune system, above all during exercise practise, as well as to show the lack of information at this respect.
A Introduction

In order to improve the performance in high competition sports, day after day new methods are developed to try to overcome the physiological limits. Therefore athletes have resorted to take substances, which not only are forbidden because they increase performance, but also they are a risk for health. These substances cause an artificial increase of the sports performance, but destabilize the physiological functions of the organism, impairing health.

Although doping is limited to sports, the intake of drugs to improve performance is also extended to many other fields, since humans in order to overcome their physical and mental limitations, resort to external substances. In Spanish society the use of medicines is spread, not only to fight against diseases, but also for anxiety, depression, tiredness, stress, pain, insomnia, etc. In the same way sportspeople take these substances to improve their performance, increase their muscular mass, improve their concentration, etc. Maybe they turn to these methods because they are under the pressure of their own ambition, coaches, federations, media and sponsors who look for greater performances in order to get higher benefits. In amateur sports there is also a big incidence of doping, they are tempted with drugs with the hope to get better results and the professional appreciation. From this social scope, it is normally forgotten or hidden the risks of these practices at short and long term. From a scientific view, nowadays the side effects of most of these drugs are known, but the studies on the matter are mainly focused in the effects on cardiovascular and nervous systems, since the aim of these studies is to know if the use of these substances can lead to death. However, little research is done about the side effects of doping substances on the immune system.

The immune system is a system of self-recognition and maintaining homeostasis. It is an extremely complex network that extends throughout the body, and it is capable of recognizing and defending the organism against pathogens. Cellular and soluble constituents of the immune system have to work in close coordination. Classically the immune system has been divided into: the innate (non-specific) response and the adaptative (specific) response. The innate response consists of macrophages and neutrophils, along with NK cells, complement and defensins, and constitutes the first line of defence. All its constituents need a basic capacity to distinguish between self and foreign. By picking up, processing and presenting antigens, macrophages form the critical link to the specific branch of the specific immune system which mainly consists in the lymphocytes and their products.
It is well known that exercise alters many immunophysiological parameters. Thus some studies have shown, that excessive exhaustive exercise is associated with symptoms of transient immunosuppression [1-10] leading to increased susceptibility to infection. Reductions in lymphocyte function include a decreased capability to produce cytokines have been observed after this type of exercise. This is particular true for athletes in a competitive setting. Since an infection would decrease athletes’ performance, and athletes are susceptible to infections, we consider it is important to know the effects of doping substances on the immune system, as well as the magnitude of these effects during training periods and competition settings. The side effects of doping substances on the immune system could be greater taking into account that most of the exercise-induced changes on this physiological system are mediated by stress hormones that can be unbalanced by the use of doping substances.

B The Immune System

In order to know the studies in this field, we did a bibliography search in the scientific database “pubmed”. We chose as keywords each prohibited substance (anabolics, narcotics, hormones and related substances, diuretics or nutritional supplements) and we match them in the following way:

- Substance + doping
- Substance + immune system
- Substance + immune system + doping
- Substance + exercise + doping

The results are shown in Figure 1. There are a lot of studies done on these substances, but it is hard to find studies which test the side effects of doping substances on the immune system.
Figure 1. Bibliography search in the scientific database "pubmed". IS= Immune system
**Stimulants**

The use of stimulants has a long history in society as well as in sports. Doping has not only been used for sports, Russian astronauts and military used stimulants as bromatan as an immune and psycho stimulant. In sports, stimulants are usually used in basketball, boxing, cycling, football, swimming and water polo. Some of the prohibited stimulants are: amphetamine, cocaine and related analogues. The effects of amphetamines and cocaine on the central nervous system are mediated through dopamine, noradrenaline and serotonin, which are all closely involved in the regulation of behaviour. Together to the psychological effects and dependence, it is known that stimulants can cause cardiovascular, respiratory, gastrointestinal and musculoskeletal diseases; but only few studies have tested the effects of these drugs on the immune system. Some of these works have observed that chronic treatment with amphetamines decreases in vitro and in vivo phagocytosis [11]. It has also been observed that cocaine induces suppression of thymus dependent T-lymphocyte response as well as increases IFN-γ production [12]. These drugs also affect the neuroendocrine system which is linked to the immune system, so alterations on the hypothalamic-pituitary-adrenal (HPA) axis would also affect the immune response, because many changes on the immune response are mediated by catecholamines and glucocorticoids. Some studies have evaluated the effects of cocaine and heroine on the HPA activation and immune response, including the release of pro-inflammatory cytokines as TNF-α. These studies showed that the immunomodulatory effects of drugs abuse, such as cocaine and opiates, affect the immune system directly as well as indirectly by also affecting the neurologic system [13].

**Narcotics**

Narcotics are well known drugs that are usually used in fight sports. Some examples of these substances are: morphine, methadone, buprenorphine, oxycodone, etc. There are used to relieve pain when there is an injury or post-surgical pain. The intake of narcotics to reduce pain can aggravate an injury because these drugs disguise pain so the athlete feels more self-confident and ignore the problem. Narcotics can be divided into 3 groups:

- Pure agonists on opioid-receptors (morphine, methadone)
- Partly agonists on opioid-receptors (buprenorphine)
- Mixed agonists/antagonists on opioid-receptors (pentazocine)
It is well known that narcotic abuse causes addiction and other psychological and physical effects such as depression, slight respiratory or nausea. In addition, opioids receptors participate in the function of immune cells due to opioid receptors have been found on the surface of different immune cells. Several evidences suggest that opioids modulate both innate and acquired immune responses. Two possible mechanisms of opiate actions have to be considered. The first one represents a direct action of the opiates through the opioid receptors on immune cells; the second mechanism would be mediated by the nervous system [14]. Thus, opioid modulation of the immune response is mediated, in part, directly through the interaction with opioid receptors expressed by one or more populations of immune cells, but the influence of opioids on the immune response is also the result of the effects of these drugs on both the central nervous system and the hypothalamic-pituitary-adrenal axis [15]. Some studies have observed that the capacity of both peritoneal macrophages and neutrophils to phagocyte the yeast Candida albicans is inhibited following in vivo administration of morphine [15-18]. These effects may be particularly dangerous for athletes during exercise, because in this situation the stimulation of innate immune responses can be crucial for preventing the entry and the maintenance of microorganism in the body [10,19]. In fact, it has been reported that exercise stimulates phagocytosis and killing of C. albicans by macrophages and neutrophils and this stimulation of phagocytes is mediated through glucocorticoids and catecholamines [20-23], this fact could be affected at the same time by narcotics. The administration of morphine in vivo also results in an atrophy of hematopoietic cells and in a reduced capacity of lymphoid cells to generate antibody in response to tetanus toxoid [15,24], which suggest that narcotics can also inhibit the adaptative response mechanism.

**Anabolic agents**

Anabolic steroids are usually synthetical derivates of testosterone. Anabolic steroids are the most used substances to increase performance and/or to improve physical appearance. These substances are usually used in athletics, bodybuilding, cycling or weight-lifting. The existence of “illegal” users and dealers of these substances, involve health risks and it makes necessary to control their toxic effects. Since 1950 till today 120 of these compounds have been synthesised, being available in the market. However, only 12 of them are used in human therapy, whereas the rest are mainly used as anabolic agents by sportspeople. The sale and use of steroid has drastically increased as a consequence of the abusive intake by athletes and by young people who take these drugs in order to improve their physical appearance. Even in the internet
you can find websites which explain how to take steroids and where to buy them.

Steroids increase protein synthesis and they can be useful in medicine, but there are so many side effects that some countries as Sweden have prohibited anabolic steroids even for therapeutic use.

There are not many studies which test the side effects of steroids on the immune system at doping concentrations. Some studies have observed that the administration of nandrolone at 10 mg/kg body weight in rats inhibited lymphocyte activity in vitro, particularly in thymus-derived cells. In this study the authors concluded that the administration of suprapharmacological doses of anabolic steroids during prolonged periods of time impairs the in vitro functionality of thymus and spleen lymphocytes [25]. Other study also observed that nandrolone and oxymetholone induced production of inflammatory cytokines, such as IL-1β and TNF-α, from human peripheral blood lymphocytes [26]. To gain a deeper insight into the effects of anabolic steroids on the immune system, further experiments are necessary to characterize other effects on cell-mediated and humoral responses.

**Hormones and related substances**

Some examples of this type of substances are erythropoietin (EPO), growth hormone, gonadothrophins, insulin or corticotrophins. They are used in basketball, cycling, bodybuilding, triathlon or volleyball. This type of substances has got a clear therapeutically use in many diseases, but have also been used by sportspeople to improve their performance, in spite of their side effects.

Maximal oxygen intake is the major performance limiting factor in endurance sports. In the last years, many recombinant EPOs have been developed. The side effects of EPO on the immune system are not still clear. Some authors suggest that artificial oxygen carriers can impair the immune system [27] or may cause severe side effects [28]. On the other hand Tu et al., [29] showed that premature rats with lower levels of red blood cell, presented a decrease in immune function, such as T cell responsiveness and TNF-α production, compared with mature rats. After the administration of recombinant human EPO, premature rats had an improved immune response.

Growth hormone (GH) has been described in general as immunosuppressive hormones [10,30]. Exogenously administrated GH is protective in many models of infection in which macrophages play important effector roles [31]. There are studies about physiological role of GH in the immune response and the
variations of this hormone following exercise, but there are no studies which link the administration of this hormone as a doping resource and its effects on the immune system. GH mediates the acute effects of exercise on neutrophils [32]. Intravenous GH injection induces a marked neutrophilia [33]. In addition an increased respiratory burst immediately after maximal exercise performed by cross-country skiers was found in parallel with increased serum GH levels [34]. However, although changes in the concentration of GH may also contribute to changes in the respiratory burst of neutrophils over repeated exercise bouts or in response to training, the results are confusing [10,35].

Diuretics

Diuretics increases diuresis. They are any substance which its chemical structure or effects are similar to those of the following substance: acetazolamide, etacrynic acid, metolazone, thiazides, triamterene, etc. Diuretics at high doses can cause loose of weight that can lead to dehydration and looses of potassium, that can cause arrhythmia even death if the lost of potassium is too high. They can also cause nausea, fatigue, fever, kidney diseases or confusion. Diuretics are usually used by bodybuilders, boxers, weight-lifters or judokas. Other athletes take these substances to disguise other prohibited substance since diuretics help to eliminate the trace of other drugs.

Some diuretics such as furosemide or spironolactone are potent inhibitors of leukocyte migration through endothelial cell monolayers [36].

Nutritional supplements

The intake of nutritional supplements is widespread in sports. The main problem of these substances is that usually they are sold as innocuous herbal derivates and in most cases they are contaminated with prohormones or other prohibited substances such as ephredines. It is, for example, the case of Ma Huang which contains ephredines that stimulate the central nervous system in the same way as amphetamines. These compounds sometimes are sold through internet, without sanitary supervision or right labelling.

The literature suggests that a heavy schedule of training and competition leads to immunosuppression in athletes, so they would be more susceptible to opportunistic infection. There are many factors which influence exercise-induced immunosuppression, and nutrition undoubtedly plays a critical role. Furthermore, inadequate or inapropriate nutrition can compound the negative
Influence of heavy exertion on immunocompetence. Dietary deficiencies of protein and specific micronutrients (iron, zinc, vitamins) have long been associated with immune dysfunction and, on the contrary excess intakes of some micronutrients can also impair immune function and have adverse effects on health [37]. As we have explained in the introduction athletes, due to strenuous bouts of prolonged exercise and heavy training, can present a depressed immune cell function. For this reason they take immunoestimulants which prevent from tissue damage caused by the exercise-induced stress. Sometimes the containers of these products do not reflect their real composition. Moreover the so called “herbal products” have sometimes immunosuppressive effects. Immunosuppressive drugs have been developed from natural products, such as soil and fungi, which are also sources of some commonly, used herbal products. However, the effect of herbal products on immune response has not yet been well investigated. Wilasrusmee et al. [38] studied the effects of some substances on lymphocyte proliferation. They observed that ginger and green tea have an immunosuppressive effect, and this effect was mediated through a decrease in IL-2 production. On the other hand, Dong quai and milk thistle increased alloresponsiveness in mixed lymphocyte culture. Other nutritional supplement frequently used is L-carnitine. It is an essential nutrient with a major role in the cellular energy production. At high doses, L-carnitine might mimic some of the biological activities of glucocorticoids, especially immunomodulation [39].

In sum, athletes may need to take some nutritional supplements in order to complement their diet, but these supplements must be supervised by physicians who also control their effects. Moreover, athletes must be cautious when they take “natural” compounds, because they can be danger to health as far as these compound can be contaminates with other harmful substances that do not appear in the label.
Table 1. *Side effects of doping substances on the immune system*

<table>
<thead>
<tr>
<th>Substance</th>
<th>Examples</th>
<th>Side effects on Immune System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolics</td>
<td>Testosterone</td>
<td>Inhibits antibody production</td>
</tr>
<tr>
<td></td>
<td>Nandrolone and other</td>
<td>↑ proinflammatory cytokines (IL-1β and TNF-α)</td>
</tr>
<tr>
<td></td>
<td>steroids</td>
<td></td>
</tr>
<tr>
<td>Peptide Hormones</td>
<td>GH</td>
<td>↑ inflammatory cytokines and free radicals production by macrophages</td>
</tr>
<tr>
<td></td>
<td>EPO</td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines</td>
<td>↓ Resistance to pathogens</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>↑ Susceptibility of infection</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>↓ Phagocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suppression of T-lymphocyte response</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Morphine</td>
<td>↓ Lymphocytes proliferation</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>↑ proinflammatory cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibits antibody response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibits macrophages and neutrophils phagocytosis</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Triamterene</td>
<td>Not clear</td>
</tr>
<tr>
<td></td>
<td>Thiazides</td>
<td></td>
</tr>
<tr>
<td>Nutritional</td>
<td>Carnitine</td>
<td>Can hide other prohibited substances as anabolics or stimulants</td>
</tr>
<tr>
<td>Supplements</td>
<td>Ma Huang Ginsen</td>
<td>Some herbal products are immunosupressive</td>
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</tr>
</tbody>
</table>
C The Skin

On the other hand, some of the side effects of these drugs on the immune system affect the skin too, as the result of an alteration of the inflammatory response. Because of this reason we will explain briefly some of the side effects of these substances on the skin.

Human skin is permanently exposed to microorganisms, but rarely infected. One reason for this natural resistance might be the existence of a 'chemical barrier' consisting in constitutively and inducible produced antimicrobial peptides and proteins [40]. Several compounds listed as illicit doping agents can express some effects on the skin. The cutaneous signs are diverse. The clue of the intake of such compounds can be supported by objective non-invasive biometrological assessments. However, such evaluations do not bring the irrefutable proof. The skin can also present unwanted reactions indicating intolerance to the doping agent. Such physiopathological manifestations are not limited to the sport competition, but can also affect some groups of the population searching for a look reminiscent of the ideal young and performing athlete [41].

A good example about how doping substances affect skin are narcotics as morphine, that frequently causes side effects such as hyperhydrosis and facial flushing, but serious cutaneous adverse drug reactions are seldom observed. Best known are urticaria, erythema, and pruritus; sometimes pseudoallergic anaphylactoid reactions and blisters are reported [42]. Morphine also has other side effects on skin as the inhibition of nociceptors of skin under inflammation conditions [43].

In connection with AAS abuse, acne may develop as the skin’s contents of cholesterol, tallow, and certain bacterial increase.

In AAS abusers, acne often spreads characteristically over shoulders and chest. A steroid pimple is usually distinguishable from a normal adolescent pimple by being larger and often sanguineous. It can also cause great pain.

When the abuse has stopped, acne will often subside but may persist for a while. More over anabolic steroids as B12 increases fulminans acne [44]. Another side effect of taking doping substances is the stretch marks. They are probably caused by hormonal changes in the skin and are seldom present in non-AAS abusers but very frequently in AAS abusers. They often occur between the large pectoral muscle and the biceps (biceps-pectoral groove), but it has been reported of their spreading on the back, thighs, and in the face.
They will remain throughout life but may fade somewhat in time. There is no effective treatment till today.

The use of ACTH or corticotrophin may cause allergic reaction, in particular in people who have a predisposition towards asthma, urticaria, eczema, etc. The non-steroid anti-inflammatory drugs (NSAIDs) have common side effects that include skin eruptions and edemas. Codeine, opiates and other derivatives can affect pruritus and Erythropoietin can cause in some cases skin reactions, allergy-like edema at the site of injection. The associated dangers’ chorionic gonadtropin (hCG) depend on dosage and according to sex, but en hombres puede mostrar allergic manifestations. The probenecid may cause dermatitis and others skin irritations.

**D Conclusion**

Athletes seem to suffer infections during and after high intensity training periods. Many research groups are studying the effects of exercise on the immune system. On the other hand there are also studies about side effects of substances which are used for doping. But there are very few studies which link the use of these substances as a doping strategy (at high concentrations and with no therapeutically purpose) and their effects on the immune system. The doping substances may impair the immune system both directly, affecting the function of immune cell, and indirectly, through the neuroendocrine system, because many of the exercise-induced changes on the immune system are mediated by neuroendocrine factors released following stress. So, the studies focused on the side effects of doping substances on the immune system are particularly important in the context of exercise-induced neuroimmunoendocrine changes. Finally, to indicate that the fact that doping substances affect the skin shows that these drugs may induce immunological reactions, however, further studies are needed.

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3.8 Psychological Effects and Addiction including CNS

Ryszard Grucza

A Motives of Doping Use by Athletes

From the beginning of human history most of the form of the rivalry has been performed with all possible means. Many events in development of human society brought clear evidence for such statement [1]. As far as sport is concerned, wherever and whenever the outcome of sporting competition has involved status, money or other similar rewards, attempts have been made to seek an advantage through doping.

Development of doping methods and substances in second half of the last century enlarged the problem of doping use in sport. Coincidence of high pharmacological technology with professionalism and commercialism in sport, rivalry of two former political systems and finally limits of human organism to drive sports results higher, created enormous pressure on athletes for better preparation for sports events and for better scientific support during training and performance. Better scientific support could also mean, for some athletes, the use of forbidden substances.

Theory of human behaviour bases on changes in social identity and individual personality in relation to understanding of current situation [2, 3]. In accordance with the theory some athletes could feel that use of banned substance would be desired or even necessary. The rush for best result and for success seems to be the main reason for using forbidden substances. Also the risk-attitude characterized for sport personality favours to accept the risk connected with doping [4]. The risk is natural and immanent part of sport and doping might be considered by an athlete as a normal cost of sport engagement.

Athletes face enormous pressure to excel in competition. Some social factors and stressing influence of sport environment can play an important role in choosing doping as a way to achieve the success. The set of “sport values”, enabling individual and social tolerance of doping, and steel acceptable by some athletes, coaches and sport managers, are presented in Figure 1.
Structures of the brain

Among the brain’s four external lobes the frontal lobe has a great meaning in development of emotions and individual character of a person. Frontal lobe is involved in planning, organizing, problem solving, selective attention, personality and a variety of "higher cognitive functions" including behaviour and emotions. The anterior portion of the frontal lobe (prefrontal cortex) is very important for the "higher cognitive functions" and determination of the personality.

The limbic system controls inborn and acquired behaviour and is a localization of instinctive behaviour, emotions and motivation. It controls the expression of emotions conveying important signals to the environment (e.g. fear, anger, discomfort, joy, happiness, etc.). Inversely, signals from the environment are closely associated to behaviour [5].

The amygdale, part of the limbic system, is a structure essential for decoding emotions, and in particular for stimuli that are threatening to the organism. The other parts of brain also project their connections to the amygdale (Figure 2).

Figure 1. Some “sport values” favouring acceptance of doping by athletes.

B Physiological Mechanisms of Behaviour and Emotion
The role of neurotransmitters

Neurotransmitters are chemicals that are used to relay, amplify and modulate electrical signals from one nerve cell to another. This occurs at a specialized cellular structure known as the synapse. The neurotransmitters diffuse across the synaptic cleft to bind to receptors which, to large extent, decide on final effect. Neurotransmitters may cause either excitatory or inhibitory post-synaptic potentials. The basic neurotransmitters and their action are presented in Table 1.

Noradrenaline, dopamine, serotonin and GABA are involved in the control of many of emotional and mental states. Most of the psychoactive drugs work by changing either their metabolism or receptor sensitivity to these neurotransmitters [6].
**Table 1. Basic neurotransmitters and their action**

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholin</td>
<td>voluntary movement of the muscles</td>
</tr>
<tr>
<td>Gamma aminobutyric acid (GABA)</td>
<td>motor behaviour</td>
</tr>
<tr>
<td>Glycine</td>
<td>spinal reflexes and motor behaviour</td>
</tr>
<tr>
<td>Glutamate</td>
<td>memory</td>
</tr>
<tr>
<td>Dopamine</td>
<td>voluntary movement and emotional arousal</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>wakefulness or arousal</td>
</tr>
<tr>
<td>Serotonin</td>
<td>memory, emotions, wakefulness, sleep and temperature regulation</td>
</tr>
</tbody>
</table>

- Noradrenaline activates nervous and motor systems. Amphetamines cause the release of noradrenaline and other catecholamine neurotransmitters.

- Dopamine has an inhibitory effect on other neurons and is strongly associated with reward mechanisms in the brain. Drugs like cocaine, opium, heroin, and alcohol increase the levels of dopamine. The nicotine brings a similar effect.

- Serotonin is involved in emotion and mood. Low level of serotonin may lead to depression, trouble sleeping and problems with anger control. Hallucinogens, such as LSD, probably act by inhibition of activity of the serotonin neurons. Antidepressant drugs help to keep a normal level of serotonin by preventing its removal from the synaptic cleft.

- GABA (gamma aminobutyric acid) exhibits inhibitory effects on excitatory neurotransmitters that lead to anxiety. Benzodiazepines enhance the effects of GABA.

Figure 3 shows a schematic model of the influence of noradrenaline, dopamine, serotonin and GABA on cognitive function, mood and emotions in man.
Figure 3. Influence of some neurotransmitters on psychical state of an organism.

The mechanisms by which the neurotransmitters elicit responses in both pre-synaptic and post-synaptic neurons are diverse. Once the molecules of neurotransmitter are released from a cell, as the result of the firing of an action potential, they bind to specific receptors on the surface of the postsynaptic cell. There are numerous subtypes of receptor for any given neurotransmitter.

Dopamine receptors play an important role in psychical state, behaviour and personality. Some studies indicate that D2-receptor may be involved in pleasure-seeking behaviour influencing the brain rewarding system. On the other hand, adventure-seeking personality, characterized by an impulsive and aggressive activity, could be attributed to type of D4-dopamine receptor [7].

Neuromodulators represent a special type of neurotransmitters, which are not reabsorbed by the pre-synaptic neuron or broken down into metabolite. Because of their longer activity in cerebrospinal fluid they can enhance or damp the overall activity level of the brain. These neuromodulators are called endogenous opioids because of they opium-like activity. The endogenous opioids include endorphins, enkephalins and dynorphins.
The reward-punishment mechanisms

Studies investigating possible mechanisms of pleasure-seeking behaviour revealed that there are some structures in the brain activated when the state of satisfaction is finally obtained by an organism. These structures work in a reward mechanism consisting of ventral tegmental area and the nucleus accumbens with cooperation of septum, amygdale, prefrontal cortex, and certain parts of the thalamus. It might be inferred that the increased dopamine release is a physiological source of satisfaction in man under sexual arousal, gambling, sport performance, etc., without any drug application [8].

Negative stimuli activate brain punishment mechanism, provoking “fight or flight” response to cope with unpleasant situation. It includes various brain structures, hypothalamus, thalamus, amygdale and hippocampus. The system functions by means of acetylcholine, which stimulates the secretion of adrenal cortico-trophic hormone (ACTH). ACTH in turn stimulates the adrenal glands to release adrenaline to prepare an organism for fight or flight response. Stimulation of the punishment mechanism can inhibit the reward mechanism [9].

There is also a third mechanism activated when both fight and flight seem impossible and the only remaining option is to behave passively. The mechanism bases on the same brain structures as for punishment mechanism with serotonin as a responsible neurotransmitter.

Fear, anxiety, aggression and pain

Fear is a strong, intense emotion experienced in the presence of a real, immediate threat, pain or danger. The neural center for fear is amygdale with influence of sensory cortex. It originates in a system that detects dangers and triggers a sequence of defensive behaviour.

Anxiety is a vague, unpleasant emotion that reflects apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria and some somatic symptoms. It can also result from imagining situations that do not really exist. The anxiety, originating in cortex, can be relieved by medications such as benzodiazepines, which increase the effect of GABA. Chronic anxiety can lead to pathological conditions.

Aggression is a form of behaviour characterized by physical or verbal attack. According to Moyer (1968) aggression has been defined as "overt behaviour with the intention of inflicting damage or other unpleasantness upon another individual" [10]. It should be noted that some aggressive behaviours can be
normal and adaptive. Most form of sport aggression may be described as an instrumental aggression which occurs in the quest of some non-aggressive goal [11].

The leading role in development of aggression has been attributed to testosterone, a male sex hormone. It is also possible, however, that some forms of human aggression, particularly violent episodic rage, may have its origin in limbic system [10]. Despite of the difference in sex hormones the neural systems modulating defensive aggression act in similar way in both males and females. This could lead to the conclusion that human aggression might have biological roots in the defensive aggression of non-primate mammals and not in hormone-dependent aggression based on testosterone [12].

Pain is a sensory modality protecting body from permanent damage. It is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is an independent sensation with its own specialized neural sensors (nociceptors), conduction pathways and centers. The most effective pharmacological way to treat the pain is application of narcotic analgesics in which the oldest representative is morphine, a constituent of opium.

C Drugs Actions

The reward mechanism and drugs

As it has been already mentioned, the pleasure centers in the brain favour behaviours that are helpful for survival. But, on the other hand, this mechanism drives people for seeking euphoria, also by using the psychoactive substances. Thus, to seek-pleasure and avoid-pain would be the mechanism responsible for taking drugs and, eventually, for the drug addiction. The risks associated with consuming a drug vary with its nature, the vulnerability of the person consuming it, the dose of drug and the time of application. For most people, abusing psychoactive substances is a learned behaviour designed to cope with some form of stress.

It is generally believed that all substances triggering dependencies in human beings increase the release of dopamine in the nucleus accumbens. The actual level of dopamine would decide, therefore, on experience pleasure, satisfaction or craving.

Different drugs increase dopamine levels in the brain in different way, either directly or indirectly. Some substances imitate natural neurotransmitters and
take place on their receptors (e.g. morphine binds to the receptors for endorphin, while nicotine binds to the receptors for acetylcholine). Other substances increase the secretion of natural neurotransmitters (e.g. cocaine mainly increases the amount of dopamine in the synapses, while ecstasy mainly increases the amount of serotonin). Still other substances block natural neurotransmitters (e.g. alcohol blocks the NMDA receptors) [9].

**Drugs dependency and addiction**

Use of substances for non-medical purpose causes a various sequence of events including psychological, physiological, pharmacological, neurobiological, social and political consequences. From the individual perspective, the flexibility and adaptability of the brain structure in response to drugs application may cause tolerance, dependency, addiction or withdrawal effects. Tolerance is one of the brain compensating mechanisms that gradually reduce the effects of drugs by change the number, or sensitivity, of the specific receptors leading to a new threshold of effective dosage. The tolerance can be associated with drug dependency defined as a persistent drug intake to prevent or diminish the physical or psychological disturbances of withdrawal (abstinence syndrome) [13]. However, the tolerance is neither a necessary nor a sufficient condition to trigger a dependency.

Physical dependency occurs when the body is deprived of drugs. Such deprivation leads to physical symptoms that vary with the drug: pain (opiates), severe tremors (alcohol), and convulsions (barbiturates and benzodiazepines). Psychological dependency can last far longer than physical dependency. It is based more on the individual's traits (habits, affective states, lifestyle) than on the substance itself. Reward system plays important role in development of psychological dependence. Cocaine and amphetamines could be good examples of substances with high psychological and low physical dependency.

Addiction to drug is a compulsive use and impaired control of intake of a drug despite of its adverse consequences [13]. The most addictive drugs are opiates, cocaine, amphetamines, alcohol and nicotine acting on reward system in the brain.

**D Psychological Effects of Doping Substances**

Contemporary medicine, physiology, biochemistry, genetics and pharmacology bring enormous possibilities to enhance sport performance. Although, drugs are
primarily designated to cure people suffering from different illnesses they are also misuse by healthy sportsmen to get an extra advantage over other competitors despite of possible short- and long-lasting negative side effects.

**Stimulants**

Stimulants (sympathomimetics) are the drugs activating central nervous system by catecholamine (adrenaline and noradrenaline) actions. Direct sympathomimetics mimic the actions of the naturally occurring catecholamines. Indirect sympathomimetics elevate the concentration of noradrenaline at neuroeffector junctions, because they either inhibit re-uptake (cocaine), facilitate release, or slow breakdown by monoamine oxidase (MAO), or exert all three of those effects (amphetamine, methamphetamine).

Stimulants are group of substances able to increase the mood and arousal, eliminate or decrease feeling of fatigue and, possibly, to enhance physical performance. In fact, the performance enhancing effects of stimulants are difficult to demonstrate. Some reports indicate that stimulants exhibit a moderate effect on performance and only when a high dose of these substances were applied. On the other hand, in contemporary sports, performance improvements amounting to less than 1% may make the difference between the gold medal and a bronze [14]. The most popular stimulants uses for doping purpose are: cocaine, amphetamine, ecstasy and methylphenidate (Ritalin). The nicotine and caffeine are also frequently used as stimulants.

Cocaine acts by blocking the re-uptake of dopamine, noradrenaline and serotonin. As a result, the natural effect of dopamine on the post-synaptic neurons is amplified. The group of such modified neurons brings a euphoria (from dopamine), feelings of confidence (from serotonin), and energy (from noradrenaline). Dependency on cocaine is closely related to its effect on the reward system. The ergogenic effects of cocaine are similar to those of amphetamines and caffeine.

Amphetamines (amphetamine and methamphetamine) are similar in structure to dopamine and act mainly by an increase in concentration of dopamine in the synaptic gap, by reducing the re-uptake of dopamine, and by excitation of dopamine sensitive neurons. Amphetamines has often been used for military and sport purposes to combat fatigue enabling sustaining attention over prolonged periods of time. Amphetamines became the drugs of choice for
athletes, particularly in sports such as cycling where these drug effects were perceived to be beneficial in enhancing sporting performance [15].

Ecstasy (MDMA) is a synthetic drug which acts simultaneously as a stimulant and as hallucinogen because of its similarity to both amphetamines and LSD. Like amphetamines and cocaine, ecstasy blocks the re-uptake of certain neurotransmitters increasing the effect of noradrenaline and dopamine. The person may then experience increased energy and euphoria.

Nicotine and caffeine are also stimulants. Nicotine is an agonist of nicotine receptors, located in the central nervous system and in neural-muscle junctions. Stimulation of nicotine receptors in ventral tegmental area enhances dopamine secretion in the nucleus accumbens. In result, the higher concentration of dopamine in the reward system contributes to development of nicotine dependency. Nicotine affects the brain quickly, like other inhalants, producing feelings of pleasure, like cocaine, and is highly addictive, like heroin.

Stimulatory effect of caffeine comes from its action on adenosine receptors, adenosine-receptor antagonist and on pituitary gland to secrete hormones enabling release of more adrenaline and driving the level of alertness. Like other stimulants, caffeine increases the production of dopamine in the brain's rewarding system. The performance enhancing effects of caffeine has not been clearly proved. Despite of its effect on the central nervous system there are, supposedly, other mechanisms including metabolic improvement and direct stimulatory action on the skeletal muscle [14].

Narcotics

Narcotics are substances causing pain relief and mood alteration in wide range from sleep and total immobilization of the body up to euphoria and over-excitation. In popular meaning the narcotics include all substances and drugs which are able to change psychical and physical status of an organism. However, in medicine the meaning of the word narcotics is limited to analgesic narcotics (opioids) which refer to all natural, semi-synthetic and synthetic substances that behave pharmacologically like morphine. Morphine, as other natural opiates, is an alkaloid derived from opium, dried juice of immature fruit capsule of Papaver somniferum. The primary medical application of morphine is to decrease the pain. The opioids, however, exert a powerful action against stress, depression and psychosis [6].

The use of pain killers is frequent in sports, especially among athletes engaged in violent activities (such as boxing for instance). Increased threshold for pain
tolerance, adjusted by narcotics application, allows for better sport performance. Additionally, narcotic analgesic may reduce anxiety, possibly enhancing performance in sport events in which excess anxiety could adversely affect fine motor control, such as pistol shooting and archery [16].

Opioids work through endogenous opioids (endorphins), enkephalins and dynorphin, modulating reactions of central nervous system to the pain stimuli. Heroin and morphine bind to the same receptors as those endogenous opioids which lead to reduced excitability of neurons, the likely source of the euphoric effect. The euphoric effect can be enlarged by involvement of GABA-inhibitory neurons of the ventral tegmental area influencing on increase of dopamine release.

It has been reported that some people with inclination to depressive mood are seeking psychological improvement through the sport. They are especially susceptible for narcotics, mainly heroin, which give a pleasure which is incomparably stronger than that obtained through intensive sports. Such psychological mechanism could lead to high risk of addiction in this group of people [17].

**Beta-2 agonists**

Activation of the sympathetic nervous system is associated with release of adrenaline and noradrenaline. These powerful neurotransmitters acts through specific receptors, called beta adrenergic receptors, located in various tissues including skeletal muscle and adipose tissue. Beta adrenergic receptors can be divided into two categories (α- and β-receptors) according to their specific response to sympathetic stimuli. Generally, the α-receptors are involved in intestinal relaxation whereas the β-receptors participate in myocardial stimulation, vasodilution and inhibition of bronchial smooth muscle. The β-receptors can be further divided to subgroups of β1 and β2, based on the receptor affinity for certain compounds.

A β-agonist can be described as a substance that stimulates the β-receptors. The most prominent representative of the β-receptor agonists are clenbuterol and salbutamol (both β2-agonists) used primarily for treatment of asthma and related bronchospasm [14]. The problem with upper respiratory airways is very common for athletes of endurance sports. This is partly due to exercise-induced bronchoconstriction related to the water and heat loss from the respiratory airways. Considering the fact that about 10-15% of Olympic athletes exhibit asthma syndromes the use of β-2 agonists is relatively high [18]. Among many
negative side effects of β-agonists application the tachycardia, nervousness, insomnia, increased blood pressure and body temperature as well as muscle tremor are most commonly observed in the users.

**Cannabinoids**

Cannabinoids are substances able to elicit psychic changes like those manifested in the course of psychosis. These substances are called as psychotomimetics, or psychedelics, or hallucinogens. Chemical structure of cannabinoids, substances obtained from Cannabis sativa (hashish and marihuana), are different comparing to natural, biogenic amines. When cannabinoids are introduced into the body, its active ingredient, delta-9-tetrahydrocannabinol (THC) modifies the function of the brain.

THC acts on the cannabinoid receptors in the brain bringing sensation of euphoria, relaxation and amplified sensory perception. The information concerning the presence of THC in the brain has been transmitted by an endogenous molecule – anandamide – bound to the cannabinoid receptors. Anandamide is involved in regulation of mood, appetite, pain, cognition and emotions. THC increases dopamine realising by compensation of inhibitory effect of GABA neurons. Chronic consumption of cannabinoids could lead to destruction of some neuron receptors in the brain (CB1) resulting in attention deficits, memory loss and impaired learning ability.

Cannabis is widely used for its altering mood and relaxation properties also in sport. Lack of scientific evidence for performance enhancing of cannabis is associated with the strong evidence of its adverse effects on psychomotor performance and cognitive function in the user. There is a growing number of young athletes using cannabinoids despite of the discipline of sport. This fact suggests that cannabinoids are not used for doping purpose but rather for social reasons [19]. However, it seems that competitors of extreme and combat sports are more susceptible for cannabinoids use than other athletes.

**Hallucinogens and inhalants**

LSD (lysergic acid diethylamide) is derived from ergot, a sugary excretion of the fungus Claviceps purpurea, which grows on rye and other grains. Recreational use of LSD became pandemic during the 1960s. LSD modifies serotonin neurotransmission by complex interaction with the 5-HT receptors. Selective serotonin re-uptake inhibitors are also reported to be involved in hallucinatory
Psychological Effects and Addiction

episodes. The exact mode of action that accounts for the peripheral, cognitive, and affective distortions remains unknown. LSD causes complex physiological changes including tremor, dizziness, headache, hypertension, tachycardia, vomiting, hyperthermia, paralysis and hyperglycemia. Among psychological and psychiatric effects the most important are: restlessness, anxiety, panic, depression, paranoia, perceptual distortions, delusions, hallucinations, visual illusions, flashbacks and prolonged psychotic reactions [20].

All inhalants can be toxic. Sniffed inhalants, such as glue, gasoline, solvents, kerosene, butyl nitrate, paint thinner, etc. exhibit almost immediate effect on the brain. Repeated use of the inhalants leads to destruction of fatty tissues protecting the nerve cells in the brain slowing down or even stops some neural transmissions. In effect a complex of physical and psychological symptoms appear among which the most typical are: muscle weakness, abdominal pain, liver, lung and kidney damage, decreases in heart and respiratory rates, nausea, nose bleeding, fatigue, headache, severe mood swings and violent behaviour, lack of coordination, mental confusion, emotional excitement and memory impairment.

Hallucinogens and inhalants are not popular doping substances because of lack of enhancing performance properties and strong psychical side effects.

CNS depressants

Drugs inhibiting activity of the central nervous system (CNS) are accidentally used in sport. The purpose of its application is calming, relaxation and good sleep. The most popular CNS depressants are benzodiazepines and alcohol.

Benzodiazepines, such as diazepam (Valium), are anxiolytics that can also have hypnotic or amnesia-inducing effects. Like alcohol, these drugs increase the efficiency of synaptic transmission of GABA. Benzodiazepines can cause a drug dependency even in therapeutic doses. Some athletes use anxiolytics to help avoid the risk of performance impairment due to lack of sufficient sleep.

Alcohol influences on membranes, ion channels, enzymes, and receptors of neurons in the central nervous system. It also binds directly to the receptors for acetylcholine, serotonin, GABA and the NMDA receptors for glutamate. In result, alcohol helps to increase the release of dopamine. In sport, the alcohol may be consumed for its potential positive effects on psychological well-being or for its tension-reduction properties. Frequent alcohol intoxication and involvement in power sports appear to be a good predictor for future anabolic-androgenic steroid abuse by an athlete [21].
**Anabolic androgenic steroids**

Testosterone, the male sex hormone, acts on central and peripheral nervous system and produces both anabolic (tissue building) and androgenic (masculinisation) effects. Anabolic-androgenic steroids are derivatives of testosterone. Applied initially for a treatment of hypogonadism, anemia and certain psychiatric disorders anabolic androgenic steroids has been widely used by elite and recreational athletes to gain strength and muscle mass, to increase the protein synthesis and the red blood cells as well as to decrease the body fat. The steroids are especially attractive in such discipline of sport like professional football, weight lifting, power lifting, bodybuilding and track and field.

Although, the application of anabolic steroids by competitive athletes has been well documented the greatest abuse of anabolic steroids has been observed in non-competitive sportsmen who take those steroids for fashionable muscular physique [22, 23]. The exact physiological mechanism of anabolic androgenic steroids enabling enhance of athletic performance has not been yet well documented and brought conflicting results [24, 25, 26].

A pattern of association between the use of anabolic-androgenic steroids and increased levels of irritability, aggression, personality disturbances and psychiatric diagnoses has been revealed in several reports [14, 27, 28]. Anabolic steroids have also been used with other harmful drugs, including tobacco, alcohol and cocaine [29]. The increased arousal and aggression may enable some athletes to train and perform more intensely. However, the high level of aggressiveness and lack of control could bring some devastating effects [30]. Some case reports indicate that using steroids with combination of amphetamine and marihuana can lead even to murder and suicide [31, 32, 33].

It should be noted that literature review on human aggression in relation to anabolic steroids misuse gives some conflicting results. Müller and Müller-Platz (2002) suggested that possible connection between anabolic steroids and aggressiveness could be restricted to “weak aggressiveness” like readiness and eagerness to compete [28, 34]. Violence and harm to others would be, therefore, exceptional. However, other reports still underlay the fact that significant psychiatric symptoms including aggression, violence, mania, psychosis and suicide have been associated with anabolic steroid abuse [32, 35].

Athletes often use other medications to hide anabolic steroids abuse or reduce the associated side effects. Anti-estrogenic agents and human chorionic gonadotropin (HCG) are usually applied to reduce gynecomastia, a potential
side effect of anabolic steroids misuse. Competitive athletes sometimes attempt to dilute their urine by taking diuretics such as furosemid or probenecid.

It has long been accepted that anabolic androgenic steroids can cause psychological dependence. The age at which sportsmen start to use steroids as well as the dose and frequency of use might be some predisposing factors. Also acceptance of alcohol, nicotine and other social drugs could favour the misuse of anabolic androgenic steroids in sports.

E Conclusion

It may be concluded that majority of doping substances used in sports cause a complex, immediate and long-lasting, changes in the central nervous system manifested by psychical and psychiatric symptoms (Tab. 2). These changes are associated with other negative side effects occurring in the body which are discussed in other chapters of the review.

It should be noted that, generally, sportsmen are not aware about the danger of psychical consequences of doping misuse and possible addiction to the drugs they apply. Also social environment with increasing acceptance of use of “recreational drugs” may favour easier use of doping substances, especially by young athletes. These facts strongly stress the needs for appropriate informative and educational programs concerning psychical side effects of doping abuse devoted to the athletes and their entourage.
**Table 2. Effects of doping substances on the central nervous system manifested by psychical and psychiatric symptoms.**

<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>EFFECTS ON CENTRAL NERVOUS SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STIMULANTS</strong></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Irritability, anxiety, paranoia, psychosis, depression, aggression, convulsions, dizziness, insomnia.</td>
</tr>
<tr>
<td>Metamphetamine</td>
<td>Irritability, aggression, paranoia, psychosis, convulsions, hallucinations, formication (the sensation of insects creeping on or under skin).</td>
</tr>
<tr>
<td>Ecstasy (MDMA)</td>
<td>Panic, anxiety, depression, paranoia, hallucinations, insomnia.</td>
</tr>
<tr>
<td>Methylphenidate (Ritalin)</td>
<td>Paranoia, hallucinations, excessive repetition of movements, headache, anxiety, delusions.</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Irritability, euphoria, psychosis, anxiety, restlessness, insomnia.</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Alertness, euphoria, reduction of fatigue.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Alertness, reduction of fatigue, anxiety, mild paranoia.</td>
</tr>
<tr>
<td><strong>NARCOTICS</strong></td>
<td></td>
</tr>
<tr>
<td>Morphine, Heroine</td>
<td>Pain relief, euphoria, lethargy, apathy, inability to concentrate, slurred speech.</td>
</tr>
<tr>
<td><strong>β-2 AGONISTS</strong></td>
<td></td>
</tr>
<tr>
<td>(Clenbuterol)</td>
<td>Nervousness, migraine, psychosis, insomnia.</td>
</tr>
<tr>
<td><strong>CANNABINOIDS</strong></td>
<td></td>
</tr>
<tr>
<td>Tetrohydrocannabinol (THC)</td>
<td>Euphoria, panic attacks, impaired comprehension, altered sense of time, paranoia, anxiety, altered cognition, impaired learning, memory, perception, and judgment, depersonalization, confusion, amnesia, hallucinations.</td>
</tr>
<tr>
<td>(Hashish, Marihuana)</td>
<td></td>
</tr>
<tr>
<td><strong>INHALANTS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache, severe mood swings and violent behaviour, lack of coordination, mental confusion, emotional excitement and memory impairment.</td>
</tr>
<tr>
<td><strong>CNS DEPRESSANTS</strong></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Sedation, decreased anxiety, amnesia</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Dizziness, hangovers, slurred speech, disturbed sleep, violent behavior, memory lapses, blackout.</td>
</tr>
<tr>
<td><strong>ANABOLIC ANDROGENIC STEROIDS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aggression, depression, mood swing, impaired memory, insomnia.</td>
</tr>
<tr>
<td><strong>HALLUCINOGENS</strong></td>
<td></td>
</tr>
<tr>
<td>PCP (phencyclidine)</td>
<td>Hallucinations, out-of-body experiences, pain resistance, disorientation, fear, panic, aggressive behaviour, depression, anxiety, paranoia, apathy.</td>
</tr>
<tr>
<td>LSD (Lysergic Acid Diethylamide)</td>
<td>Sleeplessness, recurring hallucinations, panic, dizziness, intellectual impairment, euphoria, paranoia, panic attacks, depersonalization</td>
</tr>
<tr>
<td>Mushrooms</td>
<td>Hallucinations</td>
</tr>
</tbody>
</table>
References


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4 Actual Topics of Interest

4.1 Nutritional Supplements – Creatine

Martin Schönfelder

A Introduction

The use of dietary supplements is widespread in sport worldwide and it is not limited exclusively to athletes competing at the highest level of competition. Many of these supplements are also commonly used in popular sport as well. The main reasons for using dietary supplements are to enhance physical performance, to promote health, to reduce risk of getting sick and at least to control body weight.

One of the main risk factors of dietary supplements alongside positive doping testing by contaminated supplements [1-3] is the matter of fact that a lot of sportsmen are using supplements without the knowledge of side effects and recommended intake levels. In the face of the great market of nutritional supplements (about 12 billion US$ in the USA in the year 2001) and the tremendous selling of about 3 million kilograms of creatine (Cr) worldwide in the year 2000, the edge between a recommended use and misuse is floating. Although the ergogenic potential of this naturally occurring guanidine compound was extensively studied beginning in the early 1990s [4], there are still open questions concerning health risk of long term usage of creatine.

This chapter does not purport to be an exhaustive review containing all published literature in extenso, however, this review should give a critical overview about a dietary substance which has risen on top of shopping lists of professional and popular sportsmen and which is presently not signed on the list of banned substances by the International Olympic Committee.

B Biochemistry of Creatine: From Synthesis to Storage

Cr itself was first isolated in 1832 by a French chemist named Michel Eugène Chevreul. Another scientist - Lieberg - confirmed that Cr was a regular constituent of flesh extracted from mammals. His extensive research in 1847 with wild foxes concluded that muscle work involves an accumulation of creatine. Around this time, the researchers Heintz and Pettenkofer discovered a substance in urine called creatinine (Crn). It was speculated that Crn originated from the Cr stored in muscles.
Nowadays it is known that Cr (methylguanidine acetic acid) is a derivative of amino acids which is both endogenously synthesized in the liver, pancreas, respectively the kidneys, and partly ingested by an omnivorous diet [4]. The biosynthesis, which is integrated in the arginine metabolism [5], consists of a two-step reaction which involves the amino acids glycine, arginine, and methionine (Fig. 1).

![Proposed interorgan pathway for creatine synthesis. GAA, guanidinoacetate; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine [5].](image)

In the first reversible reaction, catalyzed by L-arginine:glycine amidinotransferase (AGAT), arginine donates an amidino group to glycine to form guanidinoacetate (GAA) and ornithine. In the second irreversible step, catalyzed by the enzyme guanidinoacetate N-methyltransferase (GAMT), GAA is methylated by S-adenosylmethionine (SAM) to form S-adenosylhomocysteine (SAH) and Cr. The total body content of Cr is approximately 120 g for a 70 kg man, most of which is present in muscles and brain. Cr, respectively phosphocreatine (PCr), are liable to spontaneous, nonenzymatic cyclisation to Crn at a rate corresponds of 1.7 % of total body Cr pool. In correspondence to the total muscle mass an adult human excretes 1-2 g Crn/d.

If the source of Cr runs dry, PCr pools would be depleted in the muscle by the continuous irreversible conversion of Cr into Crn, finally excreted by the kidneys. Therefore, skeletal, cardiac and smooth muscle and brain would lose an essential component of energy metabolism. Therefore among biosynthesis, the estimated daily requirement of Cr for an average individual is about 1-2 g Cr/d.

Independent of its origin, biosynthesis or ingestion, Cr is released into the blood stream, from where it is taken up by cells, expressing the creatine transporter (CrT). This saturable sodium- and chloride dependant transporter, belonging to a transport gene family of neurotransmitters (GAT/NET), accomplish the Cr
transport against a concentration gradient in a variety of cell types [6,7]. The presence of the CrT could be demonstrated for various species by protein- or mRNA-analyses in different tissues: kidney, heart, skeletal muscle, testis, brain and colon [8-18]. Further investigations indicating the existence of mRNA transcripts in additional tissues, but the verification of its functional protein has not been conducted [7]. In addition, a few studies have reported the existence of two different mRNA transcripts and gene loci, whereby Iyer et al. have postulated that one of the genes is exclusively expressed in the testes [19]. The cellular localization of the CrT is predominantly in the plasma membrane [15,20], but there are additional evidences that the CrT protein is also located in the mitochondria. Walzel et al. showed by immunofluorescence a co-localization of CrT protein with mitochondrial markers [21]. The regulation of the CrT activity is possibly depending on the extracellular and intracellular Cr concentration, briefly reviewed in [7]. Many studies indicating, that high extracellular Cr levels, caused by a nutritional regimen, lead to an initial increase in Cr uptake and an elevated intracellular Cr concentration. Over the time, this elevated Cr concentration may feed back to inhibit the Cr uptake. Additionally, the total intracellular Cr content could be increased by co-ingestion of other nutritional ingredients, such as carbohydrates [22,23] or alpha-lipoic acid [24]; and could vary between different muscle types [25]. Furthermore, the regulation of the CrT possibly underlies certain regulatory proteins [26,27] and several hormones such as insulin and catecholamines [28], increasing the electrochemical sodium gradient across the cell membrane, which serves as the driving force of the Cr transport.

C Creatine: Metabolic Function and Physiological Mode of Action

Cr plays a key role in cellular energy metabolism and is found in metabolically active cell types such as skeletal muscle and neurons. Therefore, Cr is important for energy demand during exercise and physical activity as well as for protein synthesis that may have health or sport performance implications.

In context of the energy metabolism, all cells use the ubiquitous energy rich nucleotide ATP as predominant energy source. But according to the limited ATP stores, ATP has to be recycled by other metabolic processes. Subject to the intensity of the exercise and consequently to the energy demand, phosphocreatine (PCr) stores, anaerobic glycolysis and at least oxidative metabolism provide the regeneration of ATP [29,30]. However, it is well established that PCr stores may be more important for short lasting intensive exercise and that in most cases Cr supplementation increases total body Cr,
PCr stores and PCr resynthesis [31-33]. Energy production and interconversion of PCr and ATP is facilitated by the cellular enzyme creatine kinase CK [34]. For cytoplasmic CKs there exit three different dimeric isoenzymes, which are composed of two different monomeric subunits type M and type B: MM-CK in the muscle, MB-CK in the heart and at least BB-CK in the brain. In addition, a fourth CK isoenzyme is located in the mitochondrial membrane [35,36]. Under conditions of high intensive exercise the resynthesis of PCr could be a limited factor. The PCr pool is supposed to be an energy buffer which is involved in a creatine phosphate shuttle concept coupling glycolysis and/or oxidative processes in the mitochondria [37-39].

**Figure 2.** The phosphocreatine pathway for intracellular energy transport. ANT = adenine nucleotide translocase; CKmito and CK = mitochondrial and myofibrillar creatine kinases, correspondingly; PCr and Cr = phosphocreatine and creatine, respectively [39].

Beneath the energy demand during exercise, PCr, respectively Cr, is involved in further processes which possibly could influence or may explain the enhancement of physical performance:

- Buffering hydrogen ions (H+): H+ +PCr + ADP → Cr + ATP. This reaction may serve to attenuate the decline in pH levels during intense exercise and may delay fatigue [71]
- Metabolic regulation of mitochondrial respiration, possibly influencing oxygen kinetics during exercise [39-43]
- Alteration of gene expression of muscle myogenic factors in humans such as myogenic regulatory factor 4 or myogenin [44,45]
- Some authors postulate a possible stimulation of protein synthesis and/or anticatabolic effects respectively [46], but some negate a stimulatory effect [47,48]
- Increased satellite cell mitotic activity [49]
- Changes in myoplasmic ionic strength and total body water composition [50-52]
- Increasing glycogen stores in muscle cells [23,53-55]

D Consumption and Knowledge of Creatine

In context of the tremendous selling of Cr worldwide it would be very interesting which kind of sportsmen use Cr as a nutritional supplement or which kind of sport shows the highest incidence of its use. Table 1 illustrates an overview about studies which are engaged with the evaluation of Cr usage in different kind of sports or populations.

Own results, generated by questionnaires with in a cohort of German freshman students (n=238, mean value of age: male = 23.8y / female = 23.7), indicate that there is a tremendous lack of knowledge about nutritional supplements (Schoenfelder and Kieweg, unpublished). Only 27.7% of the asked students think that Cr gains its postulated effects, whereby 11.5% say no and 57.4% do not know anything about its effects. About 77% of all do not know the right dosage of Cr and additional 48.9% do not know the natural source of Cr. Furthermore 14.9% of the asked students think that vegetables (11.5%) or fruits (3.4%) are the natural sources of Cr. Concerning to the question of the Cr usage a sex specific distribution could be elucidated. Only 2.2% of the female students reply that they use Cr irregularly (0% regular use). In contrast, 3.5% of the male students use regularly and 10.4% use irregularly Cr as a nutritional supplement. A comparable sex specific diversity has also been shown by other authors [57,59,63,64,67].
Table 1. Evaluation of the use of creatine and nutritional supplements by questionnaires. N = responder sample sizes; NS = nutritional supplements; Cr = creatine; F = female; M = male.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>N</th>
<th>Age (y)</th>
<th>NS use</th>
<th>Cr use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuine et al. [56]</td>
<td>high school athletes</td>
<td>4011</td>
<td>16.1±1.2</td>
<td>-</td>
<td>All: 16.6% F: 3.9% M: 25.3% creatine use in all high school grades;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>usage increase with age high encouragement for Cr use by friends, coach</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and parents</td>
</tr>
<tr>
<td>Ray et al. [57]</td>
<td>high school athletes</td>
<td>674</td>
<td>15.9 (13-19)</td>
<td>-</td>
<td>All: 16% F: 2% M: 23% 26% of creatine users indicate side effects;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>creatine use in all high school grades; usage increase with age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>high encouragement for Cr use by coach</td>
</tr>
<tr>
<td>Jonnalagada et al. [58]</td>
<td>Male freshman football players</td>
<td>31</td>
<td>18.2±0.5</td>
<td>42%</td>
<td>M: 36% creatine use in all high school grades; high encouragement for</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cr use by coach</td>
</tr>
<tr>
<td>Metzl et al. [59]</td>
<td>high school athletes</td>
<td>1103</td>
<td>not asked</td>
<td>All: 5.6% F: 1.8% M: 8.8% creatine use in all high school grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>usage increase with age</td>
</tr>
<tr>
<td>Morrison et al. [60]</td>
<td>commercial gym</td>
<td>222</td>
<td>18-30; 31-45; 46+</td>
<td>84.7%</td>
<td>All: 33% Cr usage decrease with age</td>
<td></td>
</tr>
<tr>
<td>Kristiansen et al. [61]</td>
<td>varsity athletes</td>
<td>211</td>
<td>f: 20.7±1.6 m: 21.3±2</td>
<td>98.6%</td>
<td>M: 9.2% no Cr use in females</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>f: 21.9±2.8 m: 22.7±4.5</td>
<td>94.3%</td>
<td>M: 3.3%</td>
<td></td>
</tr>
<tr>
<td>Huang et al. [62]</td>
<td>Canadian athletes (Atlanta)</td>
<td>257</td>
<td>-</td>
<td>69%</td>
<td>All: 14.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canadian athletes (Sydney)</td>
<td>300</td>
<td>-</td>
<td>74%</td>
<td>All: 11.4%</td>
<td></td>
</tr>
<tr>
<td>Bell et al. [63]</td>
<td>adolescents from high school</td>
<td>333</td>
<td>15.4±1.1</td>
<td>-</td>
<td>F: 2.2% M: 7.7%</td>
<td></td>
</tr>
<tr>
<td>Sundgot-Borgen et al. [64]</td>
<td>elite athletes</td>
<td>1222</td>
<td>f: 21.4±4.6 m: 23.2±4.7</td>
<td>All: 53%</td>
<td>F: 3% M: 12%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>f: 21.9±2.8 m: 22.7±4.5</td>
<td>98.6%</td>
<td>M: 9.2% no Cr use in females</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F: 0% M: 2%</td>
<td></td>
</tr>
<tr>
<td>Greenwood et al. [65]</td>
<td>Division I collegiate athletes</td>
<td>219</td>
<td>-</td>
<td>-</td>
<td>All: 41% 89% describe positive, 38% negative and 11% no effects by Cr</td>
<td></td>
</tr>
<tr>
<td>Juhn et al. [66]</td>
<td>collegiate athletes</td>
<td>52</td>
<td>-</td>
<td>-</td>
<td>All: 75% high encouragement for Cr use by friends and team mates</td>
<td></td>
</tr>
<tr>
<td>Labotz [67]</td>
<td>varsity athletes</td>
<td>808</td>
<td>-</td>
<td>-</td>
<td>All: 28% F: 4% M: 48%</td>
<td></td>
</tr>
<tr>
<td>Mason et al. [68]</td>
<td>Male football players</td>
<td>495</td>
<td>-</td>
<td>All: 5% M: 8% All: 3% M: 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female volleyball players</td>
<td>407</td>
<td>-</td>
<td>F: 2% M: &gt;1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGuine et al. [56]</td>
<td>High school football players</td>
<td>1349</td>
<td>-</td>
<td>M: 30% creatine use in all high school grades usage increase with age</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cr use in small schools 41%, in large schools 29%</td>
<td></td>
</tr>
<tr>
<td>O’Dea [69]</td>
<td>High school athletes</td>
<td>78</td>
<td>11-18</td>
<td>-</td>
<td>5.2% 78% of the Cr users are male football players; age of Cr users is</td>
<td></td>
</tr>
<tr>
<td>Smith &amp; Duhn [70]</td>
<td>High school athletes</td>
<td>328</td>
<td>14-18</td>
<td>-</td>
<td>8.2% significantly higher than non users; high encouragement for Cr use</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>by friends; 67% of Cr users consume other supplements</td>
<td></td>
</tr>
</tbody>
</table>
E Effects and Side Effects of Creatine Supplementation

In 1999 Williams et al. [71] published an exhaustive summary on Cr supplementation and its various effects on physical performance. For 80 studies, focused effects on anaerobic power, they conclude that 50 studies showed an ergogenic effect and 42 reported nonergogenic effects and numerous studies showed both. In addition, most of the significant results were obtained in a laboratory environment but only a few field studies showed significant ergogenic results. In the context of an enhancement in prolonged (>30 to <150 sec) high-intensity tasks 12 of 22 analysed studies reported improvements in performance. Almost all reports on swim performance showed a nonergogenic effect of Cr supplementation [71]. At least the minority of studies indicate a support of efficacy of creatine in improving performance in tasks greater than 150sec in duration. Additionally, recent studies may support the opinion that Cr supplementation enhances performance in high-intensity, short-duration single or repetitive aerobic exercise. Studies on aerobic cycling exercise indicate that there exists no significant increasing in performance [72-77]. Almost all authors report no beneficial effect by Cr supplementation on blood lactate concentration, cardiovascular system or oxygen uptake. The only enhancing or modulating effects which were described are:

- lowering of plasma concentration of ammonia and hypoxanthine [72],
- significant increase of individual lactate threshold [78],
- reduced fall of blood glucose concentration during endurance exercise [73],
- Cr induced hyper-hydration can result in a more efficient thermoregulatory response during prolonged exercise in the heat [79],
- decrease in muscle inosine monophosphate [74],
- increase in fat free mass [80],
- decrease in submaximal VO2 and maximum heart rate [81].

According to the great variety of results it is necessary to perform criteria for the execution of scientific research in this field. Additionally, it is indicated to generate meta-analyses and systematic reviews to support the described beneficial results of narrative reviews. To make up the summary of Williams et al. for the years 2000 up to now in the context of power performance, an own study was set up to quantify and effects sizes (ES) for the different variables of body composition and the performance of different strength components (Schönfelder and Loeppert, unpublished). The quality assessment of the
included studies was examined on the basis of the following criteria: randomization, (double) blinding, dropouts/withdrawals, population and selection criteria, uninterpretable/intermediate results, execution of the tests, training and supplementation with their results (see Table 2). Small, but significant (p=0.05) ES were reported for body composition components: increase in body mass [BM] (0.17±0.08) and fat free mass [FFM] (0.31±0.17). The ES of percent body fat [BF] (0.04±0.01) and fat mass [FM] (-0.04±0.16) were not significantly greater than zero. ES was greater for change in BM following a loading and maintenance regimen (0.37±0.15), compared to a loading-only (0.05±0.11) or maintenance-only (0.19±0.18) regimen. There was a significant (p=0.05) ES for one repetition maximum bench press performance (0.41±0.17), but no significant ES for isometric strength of the knee extension (0.23±0.19). There were no differences in body composition or strength performance ES between males and females.

In the context of beneficial effects or no-effects of Cr supplementation the question for the side effects has also to be posed. Based on questionnaire studies (compare Chapter D) also negative effects of Cr are evident. Although most side effects are anecdotal, their evidence should not be underestimated because in context of long term usage of Cr in most cases scientific data are missing. The most described adverse effects of which are mentioned in questionnaire studies are: stomach and muscle cramps, diarrhea, nausea, dizziness, increased thirst, gastrointestinal distress and dehydration [57,65,66,118]. The fact that oral supplemented Cr reaches almost all organ systems, this nitrogenous guanidino compound could have several metabolic properties. On basis of the critical review of Juhn and Tranopolsky in 1998 [119] table 3 will sum up Cr metabolism in various organ systems and concerns regarding the effects of oral Cr supplementation.

**Table 2: Alphabetical summary of studies in context Cr supplementation, body composition and power performance in the years 2000 until now (see next page).**

| BC = Body Composition, IT = isotonic power work out, IM = isometric power work out, IK = isokinetic power workout. RDBPK = randomized, double blinded, placebo controlled; RSBPK = randomized, single blinded, placebo controlled; RDBPKX = randomized, double blinded, placebo controlled, cross over |  |
### Table 2:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>ncr</th>
<th>npl</th>
<th>nc</th>
<th>sex</th>
<th>Age</th>
<th>Population</th>
<th>Design</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmun et al. [82]</td>
<td>2005</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td>m</td>
<td>20.6</td>
<td>rugby</td>
<td>RDBPK</td>
<td>100 BC</td>
</tr>
<tr>
<td>Anciero et al. [83]</td>
<td>2001</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>m</td>
<td>7-6</td>
<td>female softball players</td>
<td>RDBPK</td>
<td>14 182 IM, IK</td>
</tr>
<tr>
<td>Ayoama et al. [84]</td>
<td>2001</td>
<td>25</td>
<td>8</td>
<td>8</td>
<td>19</td>
<td>m</td>
<td>9</td>
<td>NCAA Division I football</td>
<td>RDBPK</td>
<td>58 390 IK, IT, BC</td>
</tr>
<tr>
<td>Bemben et al. [85]</td>
<td>2001</td>
<td>19</td>
<td>11</td>
<td>8</td>
<td>20</td>
<td>m</td>
<td>11</td>
<td>untrained Sedentary working students</td>
<td>RDBPK</td>
<td>125 IM, BC</td>
</tr>
<tr>
<td>Bennett et al. [87]</td>
<td>2001</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>25</td>
<td>m</td>
<td>6</td>
<td>soldiers</td>
<td>RDBPK</td>
<td>288 IT, BC</td>
</tr>
<tr>
<td>Biwer et al. [88]</td>
<td>2003</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>f/m</td>
<td>n.b.</td>
<td>soccer</td>
<td>RDBPKX</td>
<td>141 BC</td>
</tr>
<tr>
<td>Burke et al. [90]</td>
<td>2003</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>32</td>
<td>m</td>
<td>56.1</td>
<td>healthy seniors</td>
<td>RDBPK</td>
<td>490 IM, IT, BC</td>
</tr>
<tr>
<td>Canete et al. [91]</td>
<td>2006</td>
<td>16</td>
<td>10</td>
<td>6</td>
<td>67</td>
<td>m</td>
<td>14</td>
<td>healthy seniors</td>
<td>RDBPK</td>
<td>122.4 BC</td>
</tr>
<tr>
<td>Carter et al. [92]</td>
<td>2001</td>
<td>25</td>
<td>8</td>
<td>8</td>
<td>25</td>
<td>m</td>
<td>6</td>
<td>healthy seniors</td>
<td>RDBPK</td>
<td>280 IM, IT</td>
</tr>
<tr>
<td>Cornish et al. [95]</td>
<td>2006</td>
<td>28</td>
<td>15</td>
<td>13</td>
<td>22</td>
<td>m</td>
<td>12</td>
<td>moderate active and unseasoned volunteers</td>
<td>RDBPKX</td>
<td>900 IM, BC</td>
</tr>
<tr>
<td>Eijnde et al. [98]</td>
<td>2003</td>
<td>46</td>
<td>23</td>
<td>23</td>
<td>63</td>
<td>m</td>
<td>13</td>
<td>moderate active and unseasoned volunteers</td>
<td>RDBPK</td>
<td>280 IT, BC</td>
</tr>
<tr>
<td>Falk et al. [99]</td>
<td>2006</td>
<td>26</td>
<td>13</td>
<td>13</td>
<td>24</td>
<td>m</td>
<td>6</td>
<td>Endurance trained volunteers</td>
<td>RDBPK</td>
<td>245 IT, IM, BC</td>
</tr>
<tr>
<td>Finn et al. [101]</td>
<td>2001</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>26</td>
<td>m</td>
<td>7</td>
<td>triathletes</td>
<td>RDBPK</td>
<td>100 BC</td>
</tr>
<tr>
<td>Glaister et al. [102]</td>
<td>2006</td>
<td>42</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>m</td>
<td>9</td>
<td>sport students</td>
<td>RDBPK</td>
<td>100 BC</td>
</tr>
<tr>
<td>Hoffman et al. [103]</td>
<td>2005</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>21</td>
<td>m</td>
<td>4</td>
<td>sportive active volunteers</td>
<td>RDBPK</td>
<td>36 BC</td>
</tr>
<tr>
<td>Hoffman et al. [104]</td>
<td>2006</td>
<td>33</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>m</td>
<td>4</td>
<td>college football players</td>
<td>RDBPK</td>
<td>735 IT, BC</td>
</tr>
<tr>
<td>Izquierdo et al. [105]</td>
<td>2002</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td>22</td>
<td>m</td>
<td>7</td>
<td>handball</td>
<td>RDBPK</td>
<td>100 IT, BC</td>
</tr>
<tr>
<td>Kilduff et al. [108]</td>
<td>2002</td>
<td>32</td>
<td>21</td>
<td>11</td>
<td>24</td>
<td>m</td>
<td>7</td>
<td>unseasoned volunteers in strength training</td>
<td>RDBPK</td>
<td>100 IM, BC</td>
</tr>
<tr>
<td>Kilduff et al. [107]</td>
<td>2003</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td>20</td>
<td>m</td>
<td>7</td>
<td>unseasoned volunteers in strength training</td>
<td>RDBPK</td>
<td>245 IT, IM, BC</td>
</tr>
<tr>
<td>Kilduff et al. [108]</td>
<td>2004</td>
<td>21</td>
<td>11</td>
<td>10</td>
<td>27</td>
<td>m</td>
<td>7</td>
<td>endurance trained volunteers</td>
<td>RDBPK</td>
<td>140 BC</td>
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<tr>
<td>Lehmkühl et al. [109]</td>
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<td>29</td>
<td>10</td>
<td>10</td>
<td>19</td>
<td>m</td>
<td>6</td>
<td>athletics</td>
<td>RDBPK</td>
<td>252,4 BC</td>
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<tr>
<td>Parise et al. [110]</td>
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<td>22</td>
<td>14</td>
<td>8</td>
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<td>Pfim et al. [111]</td>
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<td>36</td>
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<td>m</td>
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<td>tennis</td>
<td>RDBPK</td>
<td>195 IM</td>
</tr>
<tr>
<td>Selsby et al. [112]</td>
<td>2004</td>
<td>31</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>m</td>
<td>7</td>
<td>Endurance trained volunteers</td>
<td>RDBPK</td>
<td>25 IT</td>
</tr>
<tr>
<td>Stevenson et Dudley [113]</td>
<td>2001</td>
<td>31</td>
<td>18</td>
<td>13</td>
<td>24</td>
<td>m</td>
<td>7</td>
<td>college football players</td>
<td>RDBPK</td>
<td>140 IM, IT</td>
</tr>
<tr>
<td>Volk et al. [114]</td>
<td>2001</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>23</td>
<td>m</td>
<td>7</td>
<td>volunteers</td>
<td>RDBPK</td>
<td>172 BC</td>
</tr>
<tr>
<td>Volk et al. [115]</td>
<td>2004</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td>21</td>
<td>m</td>
<td>7</td>
<td>unseasoned volunteers in strength training</td>
<td>RDBPK</td>
<td>465,5 IT, BC</td>
</tr>
<tr>
<td>Watsford et al. [116]</td>
<td>2003</td>
<td>20</td>
<td>9</td>
<td>11</td>
<td>23</td>
<td>m</td>
<td>7</td>
<td>healthy adults</td>
<td>RDBPK</td>
<td>350 IM, BC</td>
</tr>
<tr>
<td>Wiloughby et Rosene [117]</td>
<td>2001</td>
<td>22</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>m</td>
<td>7</td>
<td>sportive inactive volunteers</td>
<td>RDBPK</td>
<td>504 IT, BC</td>
</tr>
</tbody>
</table>
Table 3. Cr metabolism in various organ systems and concerns regarding the effects of oral Cr supplementation: an update with recent studies based on Juhn and Tranopolsky [119].

<table>
<thead>
<tr>
<th>Organ system / effect</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Cardiovascular**    | No changes in cardiac muscle Cr concentration in rats (7% Cr weight); creatine feeding does not attenuate left ventricular remodelling in rat hearts post-myocardial infarction [120,121]  
No change in cardiac ejection fraction [122]  
Cr supplementation and swimming exercise stress potentially alters cardiac protein synthesis [123]  
In heart, Cr transport is determined by the content of a plasma membrane isoform of the CrT but not by the total cellular CrT pool [124]  
Dietary Cr increases cardiac muscle high energy phosphate reserves and its oxidative potential [125]  
Cr administration does not affect blood pressure neither in men nor in women [126]  
No changes in any of the echocardiographic or blood pressure measurements [81] |
| **Gastrointestinal**  | Diarrhoea and gastrointestinal pain are anecdotally reported, but no direct relationship established.  
No significant differences in the occurrence to Cr supplementation were found in context to nausea, gastrointestinal discomfort diarrhea in an 310 day trial [127]. |
| **Liver**             | Cr supplementation shows minimal or no liver enzyme elevation [128].  
Cr has no long-term detrimental effects on liver functions in highly trained college athletes [129]. |
| **Musculoskeletal**   | Because of water retention in muscle cell, there is theoretical concern about muscle cramps and tears, but causal relationship is not established [130,131]. |
| **Neurologic**        | Cr is naturally found in brain tissue. The effect of oral Cr on brain Cr concentration is unknown [132], but recent studies could indicate possible beneficial effects:  
Expression profiling showed an upregulation of genes implicated in neuronal growth, neuroprotection, and learning [133].  
Cr supplementation appears to improve high-energy phosphate turnover in healthy brain and can result in either a decrease or an increase in high-energy phosphate concentrations [134]. |
| **20g/d ingested Cr augmentation does not alter the magnetic resonance visible Cr pool in the deep frontal cerebral white matter of young active sportsmen [135].** | **Oncologic** | **Cr and PCr/Cr kinase system may influence cellular oncogenesis. Long term studies would help to determine if oral Cr is beneficial, detrimental, or has no effect on healthy subjects in this regard. [138,139].**
**Cr ingestion does not lead to increased formation of the carcinogen N-nitrososarcosine [140].**
**Anticancer effect of methylglyoxal was significantly augmented by ascorbic acid and creatine [141].** |
| **Cr supplementation had a significant positive effect on both working memory and intelligence in young, adult, vegetarian subjects [136].** | **Pediatric/adolescent** | **Theoretical concerns exist regarding extra load placed on developing kidney/other organs and the effects of creatine on muscle/bone junctions in the skeletal immature [59,142].**
**In context of high usage of Cr adolescent subjects [57] physicians, athletic trainers, and coaches should disseminate proper information and advise these adolescent athletes.** |
| **Excess consumption of Cr yields regionally dependent increases of the total Cr concentration in human brain over periods of several weeks [137].** | **Renal** | **Urinary excretion of Cr increases up to 90-fold, though glomerular filtration rate unchanged, at least during 5-day loading phase. Elevation of serum and urinary creatinine also occurs, but generally small in studies of <28 days. Concern lies with unknown effects of longer term supplementation. The results on long term effects are inconsistent.**
**Neither short-term, medium-term, nor long-term oral creatine supplements induce detrimental effects on the kidney of healthy individuals [129,143-145].**
**The use of creatine alone induced an important and significant reduction of both renal perfusion and glomerular filtration rate in rats [146].** |
| **Neither short-term, medium-term, nor long-term oral creatine supplements induce detrimental effects on the kidney of healthy individuals [129,143-145].** | **Reproductive organs** | **Cr is normally synthesized in the testes by the Sertoli cells with the seminiferous tubules. Cr and PCr are involved in sperm metabolism, but no studies exist on the effect of oral supplementation. As with liver, concern regarding reversibility of the suppression of endogenous Cr synthesis.**
**In pregnant mice, exogenous application of Cr is effective in neuroprotection. ATP as well as PCr concentrations were increased during anoxia in pups of creatine fed mice [147]. However human system remains unstudied.** |
### Creatine

| Weight gain | Proven to occur in many studies. Initially caused by water retention. With prolonged use, increased muscle synthesis may also occur [148-150]. |
| Dehydration | Intracellular fluid retention in the muscle cell may predispose to dehydration, but studies are lacking. Proper hydration during supplementation is encouraged [33]. |
| Thermoregulation | Short-term supplementation has no adverse effect on thermoregulatory responses during exercise in heat [151-158]. Cr and glycerol could be an effective method of hyperhydration capable of reducing thermal and cardiovascular responses [159]. |
| Anti aging | Median healthy life span of Cr-fed mice was 9% higher than in control mice. In brains of Cr-fed mice a trend of reduction of reactive oxygen species and significantly lower accumulation of the "aging pigment" lipofuscin; upregulation of genes implicated in neuronal growth, neuroprotection, and learning [160]. |
| Long term effects | Unknown in any human organ system. Studies involving 12 months or more are needed, preferably with larger sample sizes than previous studies. Several studies have shown that continuous Cr intake for three months or more can lead to a habituation in healthy muscle [161]. |

In summary of possible side effects of Cr supplementation, at the moment there is no scientific evidence that the short- or long-term use of Cr has any detrimental effects on otherwise healthy individuals, with exception of weight gain. This statement is also supported by several reviews recently published by Terjung and colleagues [162], Poortmans and Fanrcaux [143] and at least Bofrod and colleagues [163]. The latter formulated a position statement for the International Society of Sports Nutrition which declares that Cr supplementation “within the established guidelines is safe, effective, and ethical”. However, athletes should be educated as to proper dosing or to take creatine under medical supervision.

In this context of safety other questions arise which depends not directly on the potential health risk of excess Cr supplementation itself. Next to the fact that several nutritional supplements are contaminated with substances, e.g. non-labelled anabolic agents [1-3] - potentially leading to positive doping testing - recent reports of Benzi [164] and Yu and Deng [165] indicate additional potential cytotoxic effects. Benzi [164] mentioned that the major point related to the quality of Cr products used by humans is the amount of Cr ingested in relation to the amount of the contaminants present in the consumer products.
During the industrial process of synthetic Cr production from sarcosine and cyanamide, variable amounts of contaminants are generated; thereto belong also dicyandiamides (derivative of the starting cyanamide), dihydrotriazines (by-products of non-optimized creatine production), creatinine (by-product of industrial Cr production) and ions (such as sodium and calcium). In some cases the potential risk factors of these by-products are not clarified in detail, especially for long-term administration to human beings. Therefore, it has to be defined what is the maximal tolerable content of these substances in commercial products.

Yu and Deng [165] showed in there recent study that Cr is metabolized to methylamine, which is further converted to formaldehyde (Fig. 3) by semicarbazide-sensitive amine oxidase (SSAO). Formaldehyde is well known to cross-link proteins and DNAs. SSAO-mediated production of toxic aldehydes has been recently proposed to be related to pathological conditions such as vascular damage, diabetic complications, nephropathy, etc. [167,168]. Therefore long-term supplementation of large quantities of Cr products can increase the production of formaldehyde, which may potentially cause serious unwanted side effects.
Figure 3. Pathway of creatine metabolism by Persky and Brazeau [166]. Catalyzed by AGAT (1), catalyzed by GAMT (2), catalyzed by creatine kinase (CK) (3), spontaneous (4), catalyzed by creatine amidohydrolase (5), catalyzed by glycine oxidase (6), and catalyzed by semicarbazide-sensitive amine oxidase (SSAO) (7). Dotted pathway indicates recently hypothesized toxic formation of formaldehyde by Yu and Deng [165].
Creatine in the Context of Ethics and Doping

As manifold the described effects and potential side effects of Cr supplementation, as diverse are the opinions about Cr in context to ethics and doping. Several authors postulate that Cr supplementation is safe, effective and ethical [163]. In most case of high intensive and short duration exercise it is indisputable that Cr supplementation may bring out an increase in physical performance. But there still exist unanswered questions on health and psychological long-term effects, possible impacts on human growth, and at least the question looking forward to the “gateway theory” which is possibly related to adolescence supplement and other drug use [169]; or is it more appropriate to ask whether the Cr supplementation is “save as steak” [170]? The depicted literature suggests that oral Cr supplementation may increase muscle levels of Cr/CrP and enhance performance. But in most cases a high dose supplementation regime – approximate 20-30 g Cr per day - is necessary to gain the requested aim. Beneath commercially available Cr supplements the best natural dietary source of Cr is meat and fish. To displace just a common daily dose of 5 g Cr, for example during a maintenance regime, it is needed to eat about 1 kilogram of uncooked meat or fish; additionally Cr is unstable in heat, so cooking additively reduces the natural Cr content [171,172]. Although Cr is a naturally occurring compound and is therefore not foreign to the human body, an intake of about 30 g would appear to contravene the doping law because the amount consumed may be abnormal in comparison to normal dietary intakes and may be taken with the primary intent of enhancing performance. But currently Cr supplementation is not banned by any athletic organization, although the NCAA, the largest collegiate athletic organization in the world, enacted the ban in the year 2000 to its associated institutions that they were not allowed to provide Cr or other “muscle increasing” supplements to their athletes. Additionally, in January 2001 the France's Food Safety Agency banned the use of Cr because of potential carcinogenic risk in context of long-term supplementation. The international Olympic Committee (IOC) considered these arguments and ruled that there is no need to ban Cr supplements since Cr readily available in naturally sources. Furthermore, the IOC depict that there is still no valid test to determine whether an athlete using Cr supplements or Cr is of naturally origin [163]. In contrast to this argumentation on valid test systems, in the year 2002 Cartigny and co-workers from France published a study to discriminate between naturally ingested Cr and artificial supplements of Cr. On basis of 1H nuclear magnetic resonance (NMR) spectroscopy they presented an easy urine test as an effective tool to detect Cr supplementation [173]. Their work documented that Cr can be analysed and quantified by 1H
NMR without any pretreatment of urine samples, except for pH 5 adjustment. The results indicated that it is possible to separate between natural and artificial Cr within 24 hours after supplementation.

And if we mindfully read the “story of creatine”, we inevitably find the publication of Kalinski [174] on state-sponsored research on Cr supplementation in elite soviet sport. The countries of the former Soviet Union have a long history of research in exercise biochemistry but, because of inaccessibility of soviet journals, lack of familiarity with the language, and the secrecy surrounding this research is not well known in the West. On basis of the research of Palladin and Volkov the Central Institute of Physical Culture in Moscow initiated a long-term research program to characterize the role of Cr in muscular performance. So it could be shown that routinely given Cr led to an improvement of about 1% in 100-meter dash and 1.7% in 200m-meter sprint [174]. Of course, this was not only the practise in the former Soviet Union, but the ideology of enhancing performance by artificial substances is still evident. And we have to ask: “Is this a case of doping or is it possibly comparable to carbo loading?” And as long as it is impossible to fill up Cr stores with natural dietary sources like it works with “artificial” supplements, Cr should not be labelled as save and ethical.

G Conclusion

In today’s literature, most but not all studies depict a positive effect on short-term (less than 2 months) oral Cr supplementation on muscle in both healthy and ill humans. Additionally, Cr is indisputable one of the most used nutritional supplements in serious and popular sports, and especially adolescents may regard the use of performance-enhancing substances as an easy way to gain self-esteem through improved body appearance and athletic performance. Although many side effects are anecdotal and short-term supplementation of creatine has not been associated with major health risks, there are still existing open questions on safety and in particular the use of performance-enhancing supplements by adolescents is troubling because of the lacking safety data. On the other hand, the phenomenon of a possible habituation in healthy muscle to Cr supplementation for three months or more requires a systematic and intermittent regime of intake leaving a slight mark of “doping”. In addition, if it is not possible to fill up Cr/CrP stores with natural Cr sources, like it works with artificial Cr supplements, the question for “doping or not” is also still unanswered. Therefore, it is recommended that in this context of further studies have to clarify long-term effects under the maxim to elucidate health risk, to evaluate basis data on urinary Cr concentration in sportsmen concerning Cr
intake, and to prove and/or validate alternative techniques such as NMR spectroscopy as a tool to discriminate natural and artificial produced Cr in urine samples.

H References


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159. L. P. Kilduff, E. Georgiades, N. James, R. H. Minnion, M. Mitchell, D. Kingsmore, M. Hadjijcharlambous, and Y. P. Pitsiladis. The effects of creatine supplementation on cardiovascular, metabolic, and


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4.2 GENE DOPING

Thorsten Schulz

A Introduction

In the last decades the progress in gene technology has become a real possibility not only to treat serious diseases but also to enhance athletic performance. For this reason gene doping was included in the list of banned substances and methods of the WADA in 2003. The new prohibited list of the WADA 2008 defines gene doping as "The non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to enhance athletic performance [1]". Independent of the exigency of a gene doping definition, this definition shows a great dilemma, because every physiological and morphological adaptation in the development of organisms is based on the modulation of gene expression. Despite this all existing training methods and models include the adaptation of the body and the mind to most non-natural environmental forces in order to enhance athletic performance. Also, all ingestion (of nutrition) compromises cells, e.g. probiotics are microorganisms to enhance the colon activity or to limit the degree of exercise-induced immune depression. Creatine is able to modulate gene expression, for example of the glucose transporter 4 (see also chapter 4.1), zinc as a nutritional supplementation will influence zinc-sensitive genes and therefore the expression of these genes – is this gene doping? Strictly speaking, does this definition of gene doping lead finally to the end of the supplementation of minerals and trace-elements, the training and professional sports?

Gene expression contains the way from the gene to the protein. This includes the process of the transcription and the translation of the genes in form of the RNA and furthermore, the posttranslational modification of the protein. All these transcription and (post)translation processes incorporate manipulation factors: the question in the detection of gene doping is therefore not only if a gene is manipulated or if genetic elements are used. It is of course furthermore the way how long or often a sequence on the DNA is accessible for a DNA-polymerase, or how long a transcript is stable and how often the translation of the transcript occurs in order to build proteins is manipulated. The effects of many of the forbidden methods and substances on the prohibited list base also on the modulation of gene expression: this includes the action of the (anti-)hormones, SARMS, blocking antibodies and so on. Another question therefore is if we have a double definition for some manipulation factors?
Anyway, even if the definition is debateable, fact is that there is a great potency for gene doping, not only in future. In the following, this review will focus on discussed principles of gene doping, the status quo of the science in this area and major identified candidate genes which may enhance athletic performance through gene doping.

B Gene Technology: The Basis of Gene Doping

The definition of gene doping is based on the specific modulation of the genetic information and the expression of genes. To study, identify or modify the genes of living organisms, bio- and gene technology is used, a term that refers to a whole range of tools and techniques. This includes also techniques to transfer genetic material like DNA or RNA in order to supply possible absent components or to compensate abnormal genes. Further techniques are the sequencing of the DNA, the cloning technology, gene marker technology, transgenic techniques, and gene silencing or gene therapy. All this techniques were used by a lot of scientists like (molecular)biologists, (bio-)chemists, geneticists or medical doctors.

In broad public, gene doping is strictly associated with gene therapy, but it is more, it is the consequent appliance of gene technology. This runs from the use of specific antibodies to modify (stimulate or inhibit) gene expression to a selective modification of a cell, a gene or the modulation of a receptor to the specific regulation of gene expression after gene transfer.

Therefore, strategies to detect gene doping must have more than one focus: on the one hand it has to detect if a performance enhancement gene itself or a gene modulating construct is transferred into the body and on the other hand, if important target genes for physical performance were switched on or off with special substances.

C From Gene Transfer to Gene Doping

Athletic performance enhancement is not the intent of molecular geneticists and biochemists. There are a lot of common diseases underlying a genetic cause: a lot of cancer diseases as well as Duchenne Muscular Dystrophy (DMD), Alzheimer and Parkinson have genetic reasons. DMD, for example, is a muscle-destroying disorder that affects 1 in 3,500 young boys and typically limits their lifespan to no more than 30 years. In order to heal such disorders the idea of the “adjustment” of the dysfunctional or deleted genes was born, the gene
therapy. In short words gene therapy can be defined as an experimental technique that uses modified genes to treat or prevent disease. The most common form of the gene therapy is to insert a normal gene in a nonspecific location of the genome to replace an abnormal gene. Further approaches include

- swapping of an abnormal gene for a normal one through homologous recombination,
- repairing of an abnormal gene through selective reverse mutation, which returns the gene to its normal function,
- and altering the regulation to which a gene is turned on or off (antisense therapy).

Since 1989 more than 1300 gene therapy clinical trials have been approved worldwide, most of them, 869, in the US. But only about 2.5% of those studies were clinical phase III trials, in which more than 200 subjects were tested for a therapeutic effect. John Wiley refers the gene types transferred in clinical trials as follows [2]:

![Gene types transferred in clinical trials](image)

**Figure 1. Gene types transferred in clinical trials [2]**

To transfer the modified genes into the genome, different methods and transporters – the so-called vectors – are used. Virus-mediated gene delivery systems were differentiated from non-virus mediated gene delivery systems.
Furthermore *ex vivo* gene transfer, removed through special target cells, transfected and then transplanted back into the body and *in vivo* methods, which describe the transduction of the gene through carriers into the cells of the body were differentiated. Most common virus vectors in clinical trials are adenoviruses (AV) and retroviruses (RV) or the recombinant forms (rAV, rRV). The different viral vector systems have several unique advantages and disadvantages and therefore have special applications for which they are best suited [3]. Non-virus systems contain the injection of naked DNA in form of a plasmid or the lipofection, the injection of liposomes which carries the DNA, further the electroporation or nucleofection – the direct injection of DNA in the cell nucleus. All the non-viral vectors are relatively easy to manufacture, less costly, and have a lower toxicity as compared to viral vectors [4].

**Table 1. Vectors used in gene therapy clinical trials [2]**

<table>
<thead>
<tr>
<th>Vector</th>
<th>Gene Therapy Clinical Trials</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Adeno-associated virus (AAV)</td>
<td>48</td>
</tr>
<tr>
<td>Adenovirus (AD)</td>
<td>331</td>
</tr>
<tr>
<td>Herpes simplex virus (HSV)</td>
<td>43</td>
</tr>
<tr>
<td>Lipofection</td>
<td>102</td>
</tr>
<tr>
<td>Naked/Plasmid DNA (pDNA)</td>
<td>241</td>
</tr>
<tr>
<td>Poxvirus</td>
<td>86</td>
</tr>
<tr>
<td>Retrovirus (RV)</td>
<td>305</td>
</tr>
<tr>
<td>RNA transfer</td>
<td>17</td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>91</td>
</tr>
<tr>
<td>Other categories</td>
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<td>Unknown</td>
<td>40</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1340</strong></td>
</tr>
</tbody>
</table>

Although there is much hope for gene therapy, it is still experimental. And there are still some problems which kept gene therapy from becoming an effective treatment for genetic disease. In 1999, 18-year-old Jesse Gelsinger participated in a gene therapy trial for ornithine transcarboxylase deficiency (OTCD). It is believed that the adenoviral gene delivery triggered a severe immune response and at the end he died from multiple organ failures 4 days after starting the treatment. In January 2003 two children treated in a French gene therapy trial
using retroviral vectors in blood stem cells had developed a leukemia-like condition. So the FDA stopped temporarily all gene therapy trials. In conclusion problems are:

- **Short-lived nature of gene therapy:** the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable. There are still some problems with integrating therapeutic DNA into the genome to achieve any long-term benefits.

- **Immune response:** the possibility of stimulating the immune system in a way that reduces gene therapy effectiveness is always a potential risk.

- **Problems with viral vectors:** they include toxicity, immune and inflammatory responses, gene control and targeting issues. Furthermore, the viral vector itself may recover its ability to cause disease.

- **Multigene disorders:** they are caused by the combined effects of variations in many genes, therefore multigene or multifactorial disorders would be difficult to treat effectively using gene therapy.

Independent of the common problems of gene therapy in clinical trials and the occurrence of perilous long-term side effects, at the latest of the BALCO affair and the use of Tetrahydrogestrinone (THG) it is well known, that sportsmen use not clinically proofed substances or a pharmacological or clinical trial failed product in order to enhance performance. For this reason not only the problem of the misuse of gene therapy with the intention of doping is given, more over the use of gene technology in terms of gene doping.

### D Genes and Physical Performance: Does it Work?

In recent years, evidence is growing that physical performance is determined by genetics variants (polymorphisms). The working group around Claude Bouchard shows yearly an update of the human gene map for physical performance and health-related fitness phenotypes. A lot of possible genes are identified to influence physical performance. 2005 the gene map included 165 autosomal entries, five X chromosome assignments, and 17 mitochondrial DNA markers [5]. But in general, it seems that only a few polymorphisms (e.g. angiotensin converting enzyme ACE I/D polymorphism) or genes have the potential to really enhance performance and it is more likely that any single gene polymorphism or variant that may offer physical improvement influences the fine-tuning of performance rather than simply conferring success or failure [6].
Anyway, phenotypes of mice, cattle and humans with a special mutation in genes like myostatin, follistatin or erythropoietin receptor (EPOR) and the high performance in endurance or power of these phenotypes confirm genetic advantages. Schuelke et al. identified a myostatin mutation in a child in Berlin: at 4.5 years of age, the child had increased muscle development and strength, and was able to hold two 3-kg dumbbells with his arms extended in horizontal suspension [7]. In 1993, de la Chapelle investigated 97 members of a family with a mutation in the C-terminal part of the EPOR gene. One of the probands, Ero Mäntyranta, was one of the best crosscountry skiers in the world, winner of three Olympic gold medals and two world championships. He had a Hb level of 200 g/liter or greater since childhood and 236 g/l in the last measurement. Both, the Berlin child and Mäntyranta showed no or only harmful side effects: the motor and mental development of the myostatin mutation child has been normal and also Mäntyrantas family showed only a marked erythrocytosis with no or slight clinical implications.

E Gene Manipulation and Sports

Independent of the function of modulat ed genes, one of the most important considerations of the gene transfer is the cell specific gene delivery and the specific regulation of the genes in order to build the relevant protein.

Nowadays, there are several regulatory systems which for example control the transferred gene by gene promoters containing specific responsive elements. Those elements were induced by hormones (e.g. the antiprogestin mifepristone (RU486), the prohormone ecdysone), antibiotics (tetracycline (Tet), doxycycline), immunosupressives (rapamycine), heat shock or heavy metal ions [8; 9].

On the basis of the different transferred genes in the clinical trials, it is likely that gene transfer in sports will be used for increasing physical endurance capacity, enhancing muscle size, supporting regeneration after training and reducing the recovery for the fast resumption of training. Furthermore, training and competition associated pain and disorders will be reduced. Indeed, it is useful to cluster candidate genes for selective gene doping, but because of the complex biological function, most of the regulated genes have more than one effect.
Endurance genes

Endurance performance is strongly related to optimal tissue oxygenation and allocation of energy. This implicates an enhancement of the oxygen delivering system, e.g. the blood itself or the blood flow or the improvement of hormones regulating and proteins which modulate the energy metabolism. Targets of a gene-transfer or gene-modulation in this area include the hormonal axis e.g. erythropoietin (EPO), mitochondrial genes or receptors like peroxisome proliferator-activated receptors (PPARs), angiotensin I-converting enzyme (ACE), or hypoxia-inducible factors (HIF) and other angiogenic growth factors like VEGF or FGF.

ACE

Several studies have shown an association between ACE genotypes and athlete performance [10]. Montgomery et al. (1998) found in the first case control-study in this area an enhanced aerobic endurance performance in correlation with ACE I-alleles in British mountaineers [11]. Furthermore, the ACE D-allele is associated with impaired strength increase in the quadriceps muscle as an answer to training [12], elevated fast-twitch (FT) muscle fiber ratio [13], and better anaerobic performance [14].

Even if the present data of the polymorphisms in the ACE-allele on the athlete performance are controversial [15], there is evidence that controlling ACE is related to performance. Ondon et al. reported a positive association between use of ACE inhibitors and muscle strength and walking speed in elderly women [16]. The use of ACE inhibitors in aged rats lowered the age-related decrease in physical performance and was accompanied with a reduction in total body fat mass [17]. It is known that ACE inhibitors block the production of angiotensin II, an effective inhibitor of insulin-like growth factor 1 (IGF-1) synthesis. Long term treatment with ACE inhibitors increased serum levels of IGF-1 in the elderly [18].

ACE inhibitors and angiotensin II type I receptor blockers (ARBs) are effective therapeutic agents in the treatment of hypertension. Therefore genetic manipulation of this system in principle, might be an ideal method to attempt a genetic cure for this disease. In vivo rat models show that the use of an antisense mRNA technique successfully down-regulates transcription of the ACE and/or the angiotensin I receptor (AT1R) [19]. Already in 1999, retroviral vectors containing ACE sense and ACE antisense sequences were constructed and used in rat pulmonary artery endothelial cells. The infection of the cells
resulted in a robust expression of transcripts corresponding to ACE sense and ACE antisense. The expression of ACE-AS but not of ACE-S was associated with a permanent decrease of about 70% to 75% in ACE expression [20].

EPO

The effects of erythropoietin administration to stimulate erythropoiesis for patients [21] as well as for athletes [22] or rats [23; 24], are well documented. But dependent on the achieved hematocrit level, there are diverse effects on performance. Heinicke et al. used a transgenic mouse line (tg6) which reaches hematocrit levels up to 89% to study effects of excessive erythrocytosis. In conclusion the animals had a reduced lifespan, the exercise performance during a 120s swim test was decreased, and at age of 7 month, some animals revealed spastic contractions of the hind limb. Nerve and muscle fiber degeneration was also shown as degenerative processes in liver and kidney [25]. Eliopoulos et al. found an enhanced performance in anaemic chronic renal failure (CRF). Mice after implantation of bone marrow stromal cells (MSCs) genetically engineered to secrete pharmacologic amounts of EPO. Even if the treated animals reached a hematocrit level of about 55% that means to normal values, the animals did not reach the swimming duration of the normal control mice. In humans recombinant human EPO (rHuEPO) treatment 3 times a week for 7 weeks (20-40 IU/kg BW) improves VO₂max and running times to exhaustion with an increase in hematocrit from 44% to 49% [24]. Anyway, it is likely, that since rHuEPO became available as a performance enhancing drug, it has been misused by athletes in aerobic sports.

In anaemic patients, the EPO gene therapy is a smart option for the treatment of erythropoietic drugs: if gene therapy is able to gain balanced protein expression in vivo, on the one hand frequent injections can be eliminated and on the other hand, producing recombinant protein is not absolutely necessary any more. In vivo and ex vivo techniques for EPO gene transfer have been used. Main focus in EPO gene therapy is the regulation of EPO release in correlation to the blood haemoglobin concentration [26]. Several different methods have been used to transfer the EPO gene in order to produce the protein in the aimed tissue. In in vivo animal studies pDNA or AAV vectors were injected intramuscular or rAAV-EPO or rLV-EPO were given subcutaneous in mice and primates. Rivera et al. describes in primates after a intramuscular injection of different single AAV vectors a long term regulated gene expression of more than 6 years for EPO [27]. The system was controlled by a rapamycin
analogue for 26 cycles. In *ex vivo* gene delivery studies modified myoblasts, fibroblasts, smooth muscle cells or marrow stromal cells were used.

Electroporation-based gene transfer (electro gene transfer, EGT) is another new strategy in gene delivery. Some studies indicate that EGT is able to transfer DNA to cells through electric pulses very effectively both *in vitro* and *in vivo* [28]. In particular cells with a long lifetime e.g. muscle fibers, are of interest for a long-term expression of transferred genes. Hojman et al. could show that EGT transfer of EPO to the m. tibialis cranialis in mice led to a significant hemoglobin elevation. Furthermore, a preset level of EPO expression could be achieved by controlling the dose of inducer (doxycycline) [29].

**Peroxisome proliferator-activated receptors (PPARs)**

Recent studies could show that alterations in the PPARδ gene is associated with exercise training-induced enhancement in cardiorespiratory fitness levels in athletes [30] as well in sedentary healthy men [31]. These findings may provide evidence that PPARs are involved in physical performance. PPARs are transcription factors belonging to the nuclear receptor superfamily. Together with co-activators, they are involved in anabolic/catabolic pathways. E.g. PPARα and PPARβ/δ induce primarily genes encoding enzymes involved in fatty acid oxidation, whereas PPARγ activates genes involved in lipogenesis [32] and also plays an essential role in insulin sensitivity and adipocyte differentiation. Furthermore PPARδ is a regulatory factor responsible for muscle development.

Transgenic studies show that PPARs are possibilities for gene doping. A transgenic mouse line overexpressing wild-type PPARδ in skeletal muscle showed both development and metabolism capability of muscles by increasing fibres with oxidative metabolic capabilities. The raise was related to both hyperplasia and shifts from glycolytic to oxidative fibres and was similar of that aided by endurance training [33]. Wang et al. engineered a transgenic mouse able to run up to twice the distance of a wild-type littermate. This was achieved by a constitutively activated form of PPARδ in skeletal muscle, which promoted a switch to form high numbers of type I muscle fibers [34]. While all the described studies used transgenic mice expressing the transgene during the whole development, Lunde et al. showed with an *in vivo* transfection in normally active adult fibres that the somatic gene transfer tripled the number of I/IIa muscle fibre hybrids of a skeletal muscle, Ila fibres nearly doubled, and IIb fibres decreased [35]. Furthermore, the enzyme activity of succinate dehydrogenase was enhanced in these fibres. Even if Lunde et al. has not
evaluated these findings in a running test to show performance enhancement, he was able to show in the absence of general exercise that altering PPARδ can change muscle fibre composition, oxidative enzymes and size in muscle cells.

Further, several animal and human studies indicate that the peroxisome proliferator-activated receptor-γ coactivator 1α (PPARGC1A) gene product is also associated with endurance capacity. The PPARGC1A gene coactivates the OXPHOS genes which control oxidative phosphorylation and therefore plays a role in the development of maximal oxygen uptake (VO₂max). Anyway, Lucia et al. found that PPARGC1A genotype (Gly482Ser) predicts exceptional endurance capacity in European men [36].

**Hypoxia-inducible factors (HIFs)**

Members of the hypoxia-inducible factor (HIF) family are key mediators of genes involved in the hypoxic response. Three HIF-α subunits (HIF1-α, HIF2-α and HIF3-α) and a HIF-β subunit (with several splice variants) were identified. Only the α-subunit is in contrast to the β-subunit under control in response to changing oxygen levels [37]. However, to date more than 70 target genes involved in the response to hypoxia have been identified that are regulated by HIF-binding to hypoxia response elements (HRE) [26]. The regulated genes including those encoding for oxygen supply (e.g. EPO, vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS)), HIF control, transcription, cellular metabolism (e.g. the glucose transporters GLUT1 and GLUT3), cell growth (e.g. IGFBP1, TGF-β3) and cell death. Even though HIF-1 was identified to bind to the EPO gene via the HRE and to induce the transcription and therewith the amount of EPO, it is also interesting for misuse in sports competition because of the multitude functions in angiogenesis and glucose metabolism.

Pajusola et al. investigated the effects of VEGF vs. a stabilized form of hypoxia-inducible factor 1-α (HIF1-α) by transferring the genes via AAV gene delivery to a mouse skeletal muscle. Stabilized HIF-1α increased capillary sprouting and proliferation, the vascular perfusion in the HIF1-α treated muscles was significantly enhanced [38]. Both are factors for a better oxygen delivery and therefore performance. But independent of the HIF1-α gene delivery, administration of some drugs which activates HIF-1 may enhance physical performance as well: e.g. K-11706 inhibits GATA (a negative regulator of the EPO gene expression) binding activity, but enhances HIF-1 binding activity to the EPO enhancer. Imagawa et al. reported after administration of 3 mg/kg K-
11706 for five or eight days significantly an increased erythropoietin concentration, elevated hemoglobin concentrations, hematocrit and endurance performance in mice [39].

Because the degradation of HIF-1 is induced via hydroxylation by HIF-prolyl hydroxylases (HIF-PH), HIF-PH inhibitors (HIF-PHI) may increase EPO and red blood cell production. FibroGen has recently developed FG-2216, a HIF-PHI. Hsieh et al. reviewed that several HIF-PHI induced EPO expression in vitro and in mice, with peak EPO expression ranging from 5.6 to 207 fold above control animals [40]. In his study, chronic oral dosing of FG-2216 in male rhesus macaques was well tolerated and significantly increased erythropoeisis.

In a latest publication another gene in regard to glucose metabolism and performance enhancement was described: overexpressing phosphoenolpyruvate carboxykinase (PEPCK-C) led to a higher exercise performance in mice [41]. PEPCK-C is expressed in a number of mammalian tissues. It is involved in gluconeogenesis and the main expression occurs in white and brown adipose tissue, kidney cortex and the liver [42]. Hakimi et al. generated a transgenic mouse model, in which the PEPCK-C was expressed in skeletal muscle by linking cDNA for PEPCK-C to the $\alpha$-skeletal actin gene promoter [41]. One of the results showed that PEPCK-C$^{\text{mus}}$ mice were 7 times more active than the control animals. In detail they ran longer distances, were faster and had a up to 40% higher VO$_2$max. Furthermore, they had more mitochondria than the control animals and lived longer.

**Muscle performance enhancement via hypertrophy, hyperplasia and better regeneration**

Performance enhancement in sport is strictly addicted to adaptations of the skeletal muscle and therefore the remodeling of the myofibers. Responses of the myofibers to training include activation of intracellular signaling pathways and genetic reprogramming via endocrine mechanisms, growth factors [43] and mechanical stimuli [44] which lead as a consequence to alterations of muscle mass, contractile properties, and metabolic states [45]. Therefore, modeling hormonal status and growth factors is a target for gene therapy for people with degenerative muscle conditions. This includes for example hormones like androgens, growth hormone, insulin or growth factors like MGF, IGF, myostatin (GDF-8), TGF-β and follistatin. Also influencing factors which block or induce muscle related hormones and growth factors are relevant, e.g. decorin or IL-6 and TNFα, and therefore candidates for gene doping.
MGF/IGF/IGFBP

A key regulator in muscle mass is the growth hormone (GH) / insulin-like growth factor I (IGF-1) axis. Beside the systemic control of muscle growth by the IGFs a local one was discovered as well. Goldspink named this cryptic splice variant of IGF in the muscle, mechano growth factor (MGF) because of it’s expression in response to mechanical stimulation and the different carboxy peptide sequence to the liver type of IGF-I [46]. However, both play a role in muscle development and regeneration and show tremendous effects after alterations [46; 47]. There is evidence that in vivo both MGF and IGF-I enhance the rate of muscle protein synthesis in muscle fibers and increase proliferation of satellite cells. In different transgenic studies with naked DNA or AAV-vectors MGF cDNA and also the IGF-I liver type cDNA were inserted into muscle of normal and dystrophic mice. An increase of 15% in muscle mass and an enhancement of strength after duration of 4 months was investigated after IGF transfer. The direct MGF peptide transfer respectively injecting naked DNA intramuscular lead after a duration of 3 weeks to an increase in strength: 25% in normal and 35% in dystrophic muscle [46; 48].

Early, Scherzer et al. showed that inhibition of IGF binding proteins (IGFBPs) - which are able to bind up to 99% of IGF-I in the circulation - could lead to an increased rate of functional repair in fast-twitch muscles, evidenced by an enhanced maximum force producing capacity at 10 days after injury [49].

Growth Hormone (GH)

Doping with growth hormone has become an increasing problem since the early 1990s. Even though some studies indicate that the effectiveness of GH abuse respectively treatment in regard to performance enhancement in athletes as well as in healthy people has to be discussed [50; 51; 52]. However, GH acts through its well-known anabolic, lipolytic and antinatriuretic role, demonstrated in patients with GH deficiency or in GH deficient animal models. Besides the direct effect of GH on the peripheral tissues, there is an indirect action e.g. via the secretion of IGF-I, mostly from the liver. Anyway, it seems that only little is known about the direct action of GH on muscle and performance, e.g. GH giant transgenic mice develop large muscle fibres, GHA and GHR –/- mice build smaller muscle fibres [47]. But if those big fibres have more strength abilities is not known.

There are several gene therapy studies with animal models for the treatment of GH deficiency but till now treatment had not reached clinical phase [53].
Nevertheless, the animal models showed successful results [54], in transferring the GH gene. The GH gene delivery studies include *in vivo* and *ex vivo* models with e.g. either rAD or rAAV or naked DNA transfer techniques including the regulation of GH expression for example with rapamycine as well as *ex vivo* transfected myoblasts. In a latest report GH expression after hydrodynamic gene transfer affects different organs differently so that GH gene studies require further investigations [55].

Furthermore, increased GH secretion could be reached directly via GH releasing hormone (GHRH) or GH secretagogues e.g. the cytokine like hormone ghrelin or indirectly via leptin [56]. Khan et al. examined and discussed the effects of GHRH plasmid administration on various animal species with the presumption that this technology will reach human applications in the near future [57]. Some of the performance effects of GHRH transfer are treating anaemia, enhance immune function as well as body composition [58].

**Myostatin (GDF-8) and other members of the TGF-β superfamily**

Myostatin is a member of the transforming growth factor-β (TGF-β) family specifically expressed in skeletal muscle and is a negative muscle growth regulator. In 1997, McPherron et al. could show for the first time that modulations in the myostatin gene correlated with a phenotype of exaggerated muscle hypertrophy [59]. Several genetic studies revealed that GDF-8 mutations are responsible for the so-called ‘double muscling’ phenotype; a phenomenon almost described 200 years ago for cattle. Today, mutations for mice, sheep, cattle, dogs and humans are described [60]. Myostatin signals through activin type I and type II receptors (Alk4 and Alk5, ActR2A and ActR2B) [61]. Moreover and important in the field of doping, some endogenous peptides (see below) bind and therefore inhibit the action of myostatin. Therefore, new strategies to modulate myostatin expression or signalling could have on the one hand the possibility for treating human muscle diseases and on the other hand cheating.

Mosher et al. reported that the mutations in the myostatin gene increase muscle mass and enhances racing performances in heterozygote dogs [62]. The highest racing grade was found for 67% of the heterozygous dogs and the one homozygous mutant in contrast to 16% of the wild type dogs performed at this level. In conclusion, mutations in the myostatin alleles of these dogs showed a competitive advantage for a sprint race. Currently, only one young boy in Germany homozygote for the myostatin mutation is known. The child is unusually strong for his age; interestingly his mother is heterozygous for the
Gene Doping

myostatin mutation and was a professional sprinter [7]! In a first transgenic GDF-8 null-mice study, animals showed a 2-3 times higher muscle weight for individual muscles via a combination of hypertrophy and hyperplasia [59].

Beside the transgenic modulation, blocking of myostatin seems a useful tool of enhancing muscle growth. Bartoli et al. tested the inhibition of myostatin by AAV-mediated expression of a mutated propeptide in two animal models of two limb-girdle muscular dystrophies: In the used calpain 3-deficient mice increased muscle mass and an enhanced force was obtained [63].

MYO-029 is a recombinant human anti-myostatin monoclonal antibody to blockade myostatin activity. It is in a clinical phase I/II trial in patients with muscular dystrophy in the USA “Evaluating MYO-029 in Adult Muscular Dystrophy”, but results are not published yet. In fact, antibody-mediated myostatin blockade in mdx mice lead to enhanced muscle mass and strength [64; 65].

Acceleron Pharma's had developed a myostatin inhibitor: ACE-031. ACE-031 is a biotherapeutic based on the activin receptor type IIB (ActRIIB) and an antibody molecule that allows ACE-031 to circulate freely throughout the body. The “antibody” acts as a decoy receptor and binds myostatin before it is able to bind with ActRIIB on the surface of muscle cells. Preclinical studies with ACE-031 demonstrated that the drug directly enhances muscle mass and strength models of neuromuscular diseases. Acceleron Pharma expects to enter clinical trials with ACE-031 in early 2008 [66]! Another new approach are ALK7 decoys, which may inhibit myostatin.

Several studies concerning the administration or modulation of myostatin inhibitors like follistatin, myostatin propeptide, follistatin related protein (FLRG), Gasp-1, Titin cap, hSGT, protein ACE-031 or decorin do correlate with increased strength. Furthermore, other TGF-β superfamily related ligands normally work together with myostatin to inhibit muscle growth so that the ability for increasing muscle growth by modulating the TGF-β signalling pathway seems to be much bigger than appreciated [60]. But the effects of follistatin are controversial.

Gene ablation of follistatin could lead to skeletal and cutaneous abnormalities because activins are also members of the TGF-superfamily, affects many tissues and are inhibited by follistatin as well. Therefore, follistatin affects a lot of different tissues not only skeletal muscle [67]. Anyway recently, Nakatani et al. developed a myostatin inhibitor derived from follistatin, which does not affect activin signalling. Transgenic dystrophin-deficient mdx mice (genetic orthologue of Duchenne and Becker muscular dystrophies) with FS I-Inhibitor (FS I-I) were
generated by standard pronuclear microinjection techniques. This FS I-I transgenic mice did not show any behavioural abnormalities and reproduced normally. FS I-I transgenic mice had higher endurance capabilities than control mice up to 30% and up to 35% in strength.

**Regeneration Genes**

Injuries are the most common factors in competitive sports to reduce the training forces and the training processes. The need of fast and exact regeneration for skeletal muscle, ligaments, bone and cartilage is therefore obviously. Particularly, skeletal muscles are affected.

Decorin, a small leucine-rich proteoglycan, was shown to block TGF-β1 to improve muscle healing after injury and prevent fibrous scar formation. In decorin-treated muscles, an enhancement of muscle regeneration could be observed via histological examination [68]. Moreover, decorin may be able to up-regulate the expression of follistatin, an antagonist of myostatin (see above) [69], and may enhance expression of peroxisome-proliferator-activated receptor-gamma co-activator-1alpha (PGC-1alpha), p21, and the myogenic genes, and down-regulates TGF-β1 and myostatin. A decorin gene transfer in vivo promoted skeletal muscle regeneration and accelerated muscle healing after injury [68], suggesting that however decorin improves muscle regeneration and repair.

Usas and Huard reviewed methods with muscle-derived stem cells, which were shown to posses high myogenic capacity, regenerate both skeletal and cardiac muscle and genetically modified can differentiate into osteogenic and chondrogenic lineages to promote the repair of cartilage and bone. They report that isolated muscle-derived cells (MDCs) tolerate ex vivo manipulation well, and can be easily transduced with a variety of viral vectors [70].

A lot of growth factors are described in promoting bone healing: e.g. fibroblast growth factor (FGF), insulin-like growth factor (IGF-I, -II), platelet derived growth factor (PDGF-AA, -AB, -BB), transforming growth factor-β (TGF-β), bone morphogenetic protein (BMP), vascular endothelial growth factor (VEGF-A, -B, -E) etc. Different gene delivery systems were tested both non viral and viral; for the last system also tetracycline-based and rapamicine-based promoters regulated viral expression systems were used [4]. Anyway, the literature demonstrates the forward progress in using gene therapy for bone tissue engineering applications.
Possible Detection of Gene Doping

The discussion if gene doping is detectable exists since the debate of gene doping. Therefore, a lot of efforts were founded by the WADA to be aware of gene doping in future [1]. In 2004, the French scientific group around Lasne reported “Genetic doping with erythropoietin cDNA in primate muscle is detectable”. Anyway, a real convincing test in gene doping analytics does not exist at the moment, even if there are ambitious efforts in creating test systems on the basis of following promising strategies [71]:

1. **Modifications of proteins encoded by transgenes**: analysis of minor structural differences between the recombinant proteins expressed by the transgenes and their endogenous counterparts, possibly due to different post-translational modifications in different cells.

2. **Investigation of probable immune response to gene vectors**: because viral vectors are the most common method for gene targeting and therefore probably in gene doping as well. One possible method might be the detection of the specific immune response to viral vectors.

3. **DNA microarrays and expression profiles and molecular fingerprints**: analysis of expression profiles of endogenous genes altered by the expression of transferred or modulated genes by molecular techniques which will become more and more useful in identifying gene doping, e.g. different real time PCRs, proteomic or transcriptomic techniques and microarrays.

4. **DNA barcodes**: Manufactures may add a unique short oligonucleotide sequence to each transgene and/or viral vectors in order to detect gene doping easily. However, this approach will be based on the cooperation of all companies and scientists in the area of gene delivery and will include database maintenance with all barcodes!

Conclusion

In conclusion to this time point gene doping is – of course – not something an athlete could do in his garage; the athlete would need a lot of scientific or medical help. However, in our days, a lot of money could be earned in sports, and as the BALCO scandal taught us, there are a lot of persons who will participate in undergoing the ethical and juristic border in order to earn money or to celebrate a pharmacological or medical victory. The reviewed potential of gene doping and the today available prospects show that gene doping is not only science fiction any more.
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4.3 Narcotics

Ryszard Grucza, Andrzej Pokrywka, Dorota Kwiatkowska

A Introduction

The word “narcotic” has a different meaning in different societies and brings some misunderstanding when clear description of the drug is necessary. In popular meaning the narcotics include all substances and drugs which are able to change psychical and physical status of an organism. These changes can generally vary in effects beginning from sleep and total immobilization of the body up to euphoria and over excitation. At this same time unusual feelings and imaginations can appear altering, positively or negatively, the psychical state of a person after narcotic application. This popular understanding of the word narcotic is, therefore, more related to the symptoms observed than to the specific action of narcotic substances. In science, the narcotic effects of different substances are defined more precisely basing on their chemical structure and biological mechanisms involved in the provoked changes in human organism.

Analgesic narcotic is an addictive drug that reduces pain, induces sleep and may alter mood or behavior. The word was derived from the Greek word narkotikos, meaning "benumbing or deadening", and originally referred to a variety of substances that induce sleep (such state can be called narcosis). In some countries, narcotic refers to opium, opium derivatives, and their semi-synthetic or fully synthetic substitutes as well as cocaine and coca leaves, which, although classified as "narcotics", are chemically not narcotics. Because the term is often used broadly, inaccurately or pejoratively outside medical contexts, most medical professionals prefer the more precise term opioid, which refers to all natural, semi-synthetic and synthetic substances that behave pharmacologically like morphine, the primary constituent of natural opium. The opioids are classified on the WADA List as narcotics (Tab. 1).

The second group of substances, which are inappropriately described as narcotics, are sympathomimetics. These are generally the drugs activating the central nervous system by catecholamine (adrenaline and noradrenaline) actions. Adrenoreceptors are differentially distributed in tissues of the body and agonists at adrenoreceptors (direct sympathomimetics) mimic the actions of the naturally occurring catecholamines, and are used for various therapeutic effects. Indirect sympathomimetics are agents that elevate the concentration of noradrenaline at neuromuscular junctions, because they either inhibit re-uptake (cocaine), facilitate release, or slow breakdown by monoamine oxidase (MAO),
or exert all three of these effects (amphetamine, methamphetamine). The popular psychostimulant, methylenedioxymetamphetamine (MDMA or “ecstasy”) acutely increases neuronal dopamine and noradrenaline release bringing, as a delayed effect, a degeneration of serotonine nerve endings [1]. The substances activating the sympathetic part of the human nervous system are classified on the WADA List of prohibited substances and methods as stimulants (Tab. 1).

Table 1. Stimulants, narcotics and cannabinoids prohibited in-competition by World Anti-Doping Agency in 2007.

<table>
<thead>
<tr>
<th>SUBSTANCES AND METHODS PROHIBITED IN-COMPETITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>In addition to the categories S1 to S5 and M1 to M3 defined above, the following categories are prohibited in competition</td>
</tr>
</tbody>
</table>

**S6. STIMULANTS**
All stimulants (including both their (D- & L-) optical isomers where relevant) are prohibited, except imidazole derivatives for topical use and those stimulants included in the 2007 Monitoring Program.

Stimulants include:
Adrafinil, adrenalin, amfepramone, amiphenazole, amphetamine, amphetamine, benzphetamine, benzylpiperazine, bromantan, cathine, clobenzorex, cocaine, croprospanide, crotetamide, cyclazodone, dimethylxamphetamine, ephedrine, etamivan, etilamphetamine, ephedrine, famprofazone, fenbuzate, fencamfamin, fencamine, fenetyline, fenfluramine, fenprofazone, furfenrex, heptaminol, isometheptene, levmethamphetamine, meclofenoxate, mefenorex, mephentermine, mesocarb, methamphetamine, methylenedioxymetamphetamine, methylenedioxymethamphetamine, p-methylamphetamine, methylphenidate, modafinil, nikethamide, norfenefrine, norfenfluramine, octopamine, ortetamine, oxilofrine, parahydroxymphetamine, pemoline, pentetrazol, phendimetrazine, phenmetrazine, phenprometamine, phentermine, 4-phenylpiracetam (carphedon), prolintane, propylhexedrine, selegiline, sibutramine, strychnine, tuaminohettane and other substances with a similar chemical structure or similar biological effect(s).

**S7. NARCOTICS**
The following narcotics are prohibited:
buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, pethidine.

**S8. CANNABINOIDS**
Cannabinoids (e.g. hashish, marijuana) are prohibited.
The third group constitutes substances able to elicit psychic changes like those manifested in the course of psychosis. These substances are called psychotomimetics or psychedelics or hallucinogens. Since different psychotomimetics exhibit different actions on the central nervous system the mechanism of the psychotogenic effects remains unclear. Some hallucinogens such as LSD, psilocin, bufotenin, and mescaline bear a structural resemblance to serotonin, natural biogenic amine playing a neuromediator function in the central nervous system. Conversely, the structure of other substances such as tetrahydrocannabinol from Cannabis sativa (hashish and marihuana), muscimol or phencyclidine is different comparing to biogenic amines. Among the psychotomimetics only the cannabinoids were located on the WADA list of prohibited substances and methods as a separated group of substances (Tab. 1).

B Analgesic Narcotics (Opioids)

Background

Ideographs of the ancient Sumerians suggest that psychological effects of opium may have been known around 4000 B.C. The Egyptians described the medicinal value of the opium poppy in 1552 B.C. However, the first reference to the actual juice of the poppy appeared in the 3rd century B.C. writings of Theophrastus. The term opium is derived from the Greek word for juice and refers to the juice of the poppy capsule. Opium appeared in Western Europe in XI and XII centuries. In XVI century Paracelsus composed laudanum – a mixture of opium, wine and spices. The laudanum is still used today to treat a variety of ailments [2].

Periodic reports describing the use by athletes of caffeine, strychnine, opium, ether and alcohol appeared between the middle of the nineteenth century and the advent of the Second World War [3]. However, the main applications of substances considered today as doping agents were exercised during numerous military conflicts between different countries. The opioids were especially popular in XIX century in USA and Germany where they were widely used by soldiers and brought some social problems after the wars (Tab. 2).
Table 2. Doping use for military purpose.

<table>
<thead>
<tr>
<th>Year</th>
<th>War</th>
<th>Substance or Method</th>
<th>Purpose</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1718</td>
<td>Norway-Sweden</td>
<td>Amanita muscaria</td>
<td>Stimulation</td>
<td>Norway, Sweden</td>
</tr>
<tr>
<td>1863</td>
<td>Civil War</td>
<td>Morphine</td>
<td></td>
<td>USA</td>
</tr>
<tr>
<td>1883</td>
<td>Germany-France</td>
<td>Heroine</td>
<td></td>
<td>Germany</td>
</tr>
<tr>
<td>1939-1945</td>
<td>World War II</td>
<td>Amphetamine (“Benzendrine”)</td>
<td>Stimulation (over 72 mln “energy tablet”)</td>
<td>Great Britain, USA</td>
</tr>
<tr>
<td>1939-1945</td>
<td>World War II</td>
<td>Ephedrine, methamphetamine</td>
<td>Stimulation</td>
<td>Germany</td>
</tr>
<tr>
<td>1939-1945</td>
<td>World War II</td>
<td>Testosterone</td>
<td>Aggressiveness</td>
<td>Germany</td>
</tr>
<tr>
<td>1939-1945</td>
<td>World War II</td>
<td>Blood transfusion</td>
<td>Adaptation to high attitude in pilots</td>
<td>Germany</td>
</tr>
</tbody>
</table>

Even that the opium was widely used during the recent four centuries for its hypnotic and analgesic properties the pure morphine was extracted in 1803 by the German pharmacist Friedrich Wilhelm Sertürner. The codeine, another alkaloid derived from opium, was discovered 29 years later by Pierre Jean Robiquet. Codeine will be discussed in contrast to morphine since this is a drug exhibiting a low level of addiction when applied to patients. From this reason codeine is widely used in medicine and has not been banned in sport. Morphine is a main alkaloid derived from opium, dried juice of the immature fruit capsule of *Papaver somniferum*, and used as an analgesic narcotic drug [4]. Codeine is another opium alkaloid applied as a antitussive and analgesic drug. Codeine is classified as a relatively mild analgesic. It is frequently used clinically in combination with other analgesic and as a cough suppressant [5]. The chemical structure of both morphine and codeine is presented in Figure 1.

![Chemical structure of morphine and codeine.](image-url)
The primary medical application of morphine is to decrease the pain. Based on the theory of Beckett (1957) it has been experimentally proved that a specific opioid receptors exists, located in some structures of the brain. These receptors differ in pharmacological properties, localization and in specific responses to different opioid peptides (Tab. 3).

**Table 3. Some receptors of the central nervous system with specific reactivity to opioid peptides.**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
<th>Endogenous opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>Analgesic, respiratory depression, constipation, euphoria</td>
<td>Endorphin</td>
</tr>
<tr>
<td>δ</td>
<td>Analgesic</td>
<td>Enkephalin</td>
</tr>
<tr>
<td>κ</td>
<td>Dysphoria</td>
<td>Dynorphin</td>
</tr>
</tbody>
</table>

Morphine and codeine are the natural fenantren alkaloids present in opium and, as remaining about 20 other alkaloids, are derived from a premature poppy capsule (*Papaver somniferum*). The content of opium in the poppy capsule depends on the climatic conditions and on the form of the poppy cultivation. It usually varies between 3-23% (10% on average) for morphine and between 0-6% (0.2% on average) for codeine. The content of izochinoline alkaloids varies from 1.5% to 12% (10% on average) for noscapine (narcotine) and from 0.1% to 4.5% (5% on average) for papaverine. In general, the fenantren derivatives of opium exhibit analgesic properties while the isochinoline derivatives exhibit spasmyloytic properties [6].

The opiate receptors are located in both the central nervous system and the periphery [5]. However, the predominant effect of opioids is the partial modification of the activity of the central nervous system. The peripheral action of analgesic narcotics is partly related to the effects of histamine release following the narcotics application (Tab. 4).
Table 4. Central and peripheral action of analgesic narcotics.

<table>
<thead>
<tr>
<th>CENTRAL</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief (analgesia)</td>
<td>All sorts of pain</td>
</tr>
<tr>
<td>Calming</td>
<td>Drowsiness, decreased concentration, mental clouding</td>
</tr>
<tr>
<td>Dysphoria (at the beginning of application)</td>
<td>Decreased physical activity, lethargy</td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Prolonged pauses between breaths, periodic breathing; after opioid overdose – death due to respiratory arrest</td>
</tr>
<tr>
<td>Anti caught action</td>
<td></td>
</tr>
<tr>
<td>Decreased volume of urine</td>
<td>Modification of hormonal activity in hypophyseal-hypothalamic axis</td>
</tr>
<tr>
<td>Decreased body temperature</td>
<td>Depressing action on hypothalamus</td>
</tr>
<tr>
<td>Nausea and vomiting (at the beginning of application)</td>
<td>Activation of vomiting centre</td>
</tr>
<tr>
<td>Decreased tremor level of muscles</td>
<td>Augmenting activity of inhibitory neurons mediated by benzodiazepine receptors (GABA)</td>
</tr>
<tr>
<td>Narrowing the pupils</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Effect on vagal nerve</td>
</tr>
<tr>
<td>Physical and psychical</td>
<td></td>
</tr>
<tr>
<td>dependence</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PERIPHERAL</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peristalsis, constipation, biliary colic, urinary tract obstruction</td>
<td>Increased tension of smooth muscles</td>
</tr>
<tr>
<td>Bronchial spasm</td>
<td>Effect of histamine release</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Vasodilatation – effect of histamine release</td>
</tr>
<tr>
<td>Inhibiting of uterus muscles tension</td>
<td>Birth process prolongation – effect of histamine release</td>
</tr>
</tbody>
</table>
C Clinical, Pharmacological and Biological Function of Analgesic Narcotics

Clinical application

The drugs based on opium act only symptomatically. The main, medical reason of its application is analgesic (pain killing). When applied, the balance of positive and negative effects of the opioids on an organism should be considered.

Form of application

Morphine is primarily applied by injection. Oral use of morphine causes a decreased biological availability because of its elimination by liver immediately after absorption. The analgesic effect of morphine taken orally is about of one-tenth of the effect produced by subcutaneous injection.

Pharmacokinetics

With a standard dose of 10 mg of morphine a maximum analgesic effect is observed after 20-30 min of intravenous injection and after 60-90 min of intramuscular injection. The anti-pain effect lasts 3-4 h and 4-5 h, respectively.

Body distribution

Morphine penetrates the central nervous system moderately. Derivatives of morphine are easier accepted by CNS (i.e. monoacetylmorphine – MAM) than pure morphine. Greater concentration of morphine can be found in kidneys, liver, lungs and spleen.

Metabolism

Morphine does not cumulate in the organism. It appears in the urine during 30 min after application. About 50 % of the dose is excreted during 8 h. After 24 h over 90 % of the morphine dose is removed from the organism. The main metabolic process (about 70 %) is taking place in liver and consists of the junction of morphine and its metabolites with glucuronid acid.

Symptoms of acute intoxication by opioids

Intoxication by opioids is associated with following symptoms: narrowing the pupils, drowsiness, coma, dry and cool skin, breathing disturbances (Cheyne-Stokes breathing) up to the inhibition of respiration, decreased heart rate, blood pressure and body temperature. Death can appear in result of respiratory and cardiovascular insufficiency immediately after intravenous injection of morphine or during 2-4 h after oral application of morphine.
**Opioids addiction**

Opioids are the drugs with a great potential of physical and psychical dependence. Tolerance to morphine develops quickly. However, heroine (diacetylmorphine) penetrates into the central nervous system much faster than morphine, developing dependence in a very short time. In contrast to heroine, codeine, generally, does not cause physical or psychical dependence. There is a long list of adverse effects of opioid addiction. The most important ones are:

- damage of soft tissues (mainly liver)
- hormonal deregulation (especially water balance control)
- disturbances in immunological function
- organism devastation
- inflammatory changes in skin, and in venous and lymph tubes
- needle sharing (infection, hepatitis B, HIV)
- sexual problems
- constipation

**Mechanism of opioids addiction**

Some studies indicate that opioids, cannabinoids and cocaine may affect the same reward centers in the central nervous system systems as alcohol and nicotine. The dependence syndrome occurs with heavy chronic use in individuals who report problems in controlling their use and who continue to use the drug despite experiencing adverse personal consequences. Estimated risk of dependence development is about 32 % for nicotine, 23 % for opioids, 15 % for alcohol and over 10% for cannabinoids [7].

**Abstention syndrome**

Sudden withdrawal of opioid drugs or application of opioid antagonists causes a withdrawal syndrome in an addicted person. The withdrawal syndrome can appear just after 8 h and last 7-10 days. The maximum of negative symptoms is observed during 2-3 day of abstention. Opioid hunger is hardly tolerated by patients who can exhibit the following symptoms:

- increase in heart rate, blood pressure and body temperature
- sweating, heat flashes
- muscle tremor, spasm and pain
- piloerection
- sleeplessness, dizziness, restlessness
- nausea, vomiting, diarrhea
- yawning
- drug-seeking behaviour

D Narcotics and Sport

Narcotics were indicated on the first list of banned substances in sport prepared by the International Olympic Committee (IOC) in 1967. Currently, as it has been mentioned above (Tab. 1), the World Anti-Doping Agency (WADA) located narcotics in categories of substances prohibited in competition only. The number of prohibited substances in this category is closed and restricted to the substances directly mentioned on the list. The concept of the doping list is the prohibition of substances and methods which can positively affect athletic performance, which might have a negative impact on health, and which are contrary to the spirit of sport [8].

Narcotics are often treated as non ergogenic drugs nor the drugs enhancing physical performance. This is a controversial attitude towards narcotics because their potential use in sports might be of some importance allowing athletes to perform competitively despite of various musculoskeletal injuries [2, 9]. As shown in Figure 2, the increased pain threshold, adjusted by narcotics application, allows for better both pain tolerance and exercise performance. In result of the decreased inhibitory effect of pain the greater effort exerted by the athlete could lead to some injuries and damages in the athlete organism. The described mechanism fully complies with all elements of the concept of doping.

Figure 2. Simplified representation of the basic mechanism of enhancing performance with increased tolerance to pain by analgesic narcotics, which can lead to damage in the athlete organism.
The use of pain killers is frequent in sports, especially among athletes engaged in violent activities (such as boxing for instance). Often, the fear of losing a place or not fulfilling a contractual obligation leads to an obsession to keep the fight in spite of any type of wound or handicap. The most common effect of this class of substances is sedation, providing that habitual doses are used [10]. Additionally, narcotic analgesic may reduce anxiety, possibly enhancing performance in sport events in which excess anxiety could adversely affect fine motor control, such as pistol shooting and archery [11].

These drugs are banned both to limit the potential abuses that may lead to career ending injuries and to reduce the risk for tragic addictions. The death of Baltimore Colts great “Big Daddy” Lipscomb, caused by heroin addiction in 1963, still serves as one of the most infamous examples of a narcotic related tragedy [12]. Also Poli Diaz, an eight time European Lightweight Champion, ended his professional career hooked on heroin. Recently, former French cyclist Laurent Roux was convicted of supplying a drug mix known as “the Belgian pot” reported to include cocaine, heroin and amphetamines to cyclist.

It has been found that there exists a significant association between doping agents using and acceptance of narcotics. In the study of Pedersen (2001) 8.3% of doping users used also amphetamines, 14.2% MDMA, and 30.3% heroin [13]. Thus, it might be concluded that some people exhibit a psychical susceptibility to accept all sort of external drivers beginning from tobacco and alcohol and ending on doping agents and narcotics.

The presence of narcotics and cannabinoids on the WADA list of prohibited substances is a subject of some controversy. According to Kindermann (2004) the use of illegal drugs like heroin and cannabinoids should better be addressed as "unsportsmanlike" behaviour and punished on the basis of regulations separate from the doping list [8]. The Netherlands Anti-Doping Organization presented similar opinion in comments on the proposed WADA Prohibited List for 2005. In their opinion, the entire group of narcotics should not be part of the prohibited list. The inclusion of this group in the prohibited list is far more likely to do harm to the anti-doping efforts than the chances that it will protect fair play and the health of athletes. Similarly, cannabis use, however objectionable it might be, should not be regarded as doping use [14].

Contrary to cannabinoids the analgesic narcotics are not often used by athletes and whenever they are misused, it is rather a case of malpractice than intended doping application. In the period 2001-2005 opioids were detected only in 0.1% of total samples analyzed in all IOC and WADA accredited laboratories. At the
same time the relative contribution of positive samples with cannabinoids was 0.27 % (Tab. 5).

Table 5. Narcotics and cannabinoids detected in IOC and WADA accredited laboratories [AL] in the years 2001-2005.

<table>
<thead>
<tr>
<th>Year</th>
<th>AL</th>
<th>Samples</th>
<th>Narcotics</th>
<th>% Narcotics</th>
<th>Cannabinoids</th>
<th>% Cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>25</td>
<td>125,701</td>
<td>29</td>
<td>0.02</td>
<td>298</td>
<td>0.24</td>
</tr>
<tr>
<td>2002</td>
<td>26</td>
<td>131,373</td>
<td>13</td>
<td>0.01</td>
<td>347</td>
<td>0.26</td>
</tr>
<tr>
<td>2003</td>
<td>31</td>
<td>151,210</td>
<td>26</td>
<td>0.02</td>
<td>378</td>
<td>0.25</td>
</tr>
<tr>
<td>2004</td>
<td>32</td>
<td>169,187</td>
<td>15</td>
<td>0.01</td>
<td>518</td>
<td>0.31</td>
</tr>
<tr>
<td>2005</td>
<td>33</td>
<td>183,337</td>
<td>17</td>
<td>0.01</td>
<td>503</td>
<td>0.27</td>
</tr>
<tr>
<td>Years 2001-2005</td>
<td>760,808</td>
<td>100</td>
<td>0.01</td>
<td>2,044</td>
<td>0.27</td>
<td></td>
</tr>
</tbody>
</table>

The majority (81%) of the 100 examined samples with different narcotics contained morphine. The other substances were pethidine (6%), methadone (5%), hydromorphone (3%), oxycodone (2%), buprenorphine, dextromoramide and hydrocodone (each by 1%).

It should be noted that, according to the WADA regulations, out-of-competition samples are not tested for narcotics and cannabinoids. This type of samples account for approximately of 50% of the total number of samples. Thus, it might infer that the real number of samples containing opioids and cannabinoids can be much greater than that reported by IOC and WADA accredited laboratories. Among 9061 urine samples tested in the Department of Anti-doping Research in Warsaw during the years 2001 to 2005, only 4 cases with analgesic narcotics were found (Tab. 6). At the same time 102 samples containing cannabinoids (carboxy-THC > 15 ng/ml) were detected.

Table 6. Analgesic narcotics detected in urine samples in the Department of Anti-doping Research, Institute of Sport Warsaw during recent 5 years.

<table>
<thead>
<tr>
<th>Year</th>
<th>Substance</th>
<th>Gender</th>
<th>Age</th>
<th>Sport</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Morphine &gt;1μg/ml, Nandrolone 4.9 ng/ml</td>
<td>Male</td>
<td>26</td>
<td>Water motor sports</td>
</tr>
<tr>
<td>2001</td>
<td>Morphine &gt;1μg/ml</td>
<td>Male</td>
<td>21</td>
<td>Cycling</td>
</tr>
<tr>
<td>2001</td>
<td>Morphine &gt;1μg/ml</td>
<td>Female</td>
<td>20</td>
<td>Fencing</td>
</tr>
<tr>
<td>2005</td>
<td>Hydromorphone</td>
<td>Female</td>
<td>18</td>
<td>Cycling</td>
</tr>
</tbody>
</table>
Poppy seeds consumption and doping detection

Poppy seeds are popular ingredients of some cakes in many countries. However, consumption of such a cake may cause morphine appearance in the body. As it has been shown by Thevis et al. (2003) consumption of typical cake containing poppy seeds or baking mixtures brought in result morphine concentrations in urine greater than 1 µg/ml, with a peak value of about 10 µg/ml [15]. Similar effects of morphine concentration in urine were observed by Van Thuyne et al. (2002) after administration of two Papaveris fructus containing herbal teas to five male volunteers. Maximum morphine concentrations, 4.3 and 7.4 µg/ml, respectively, were obtained 4-6 h after administration [16]. Under such circumstances the established cutoff limit for morphine concentrations in human urine equal to 1 µg/ml is disputable since the poppy seeds consumption may lead to an unintentional doping case.

Codeine and doping detection

Some studies indicated also a possible occurrence of morphine in human organism caused by metabolism of allowed medicines containing codeine. Codeine, after oral administration, is metabolized in the liver to morphine, norcodeine and its conjugates. Results of investigations performed by Delbeke and Debackere (1991) clearly showed that application of antitussive drugs (tablets or syrups) may result in appearance of morphine concentrations in urine greater than 1 µg/ml, thus to provoke an adverse analytical finding in anti-doping laboratory [17].

E Conclusion

Analgesic narcotic is a highly addictive drug that reduces pain, alters mood or behavior and causes various health effects. Furthermore it exhibits a potential to enhance performance by increased tolerance to pain and reduced anxiety. This damped physiological reactivity to increased pain can lead to damages in athlete organism during strenuous exercise. But the number of doping cases by analgesic narcotics is relatively small. Excessively so, there is a higher risk of unintentional doping by consumption of poppy cakes or application of allowed medicines containing codeine. Therefore, the cutoff limit for morphine concentrations in human urine equal to 1 µg/ml should be revised.
F References


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4.4 Cannabinoids

Peter Van Eenoo, Frans T. Delbeke

A. Introduction

Cannabinoids are a group of active substances present in the plant Cannabis sativa L. There are mainly two types of this plant, Cannabis sativa sativa (regular hemp) and Cannabis sativa indica (Indian hemp). For use as a narcotic Cannabis sativa indica is of outmost interest. The resin, flowers, leaves and other parts of this plant contain a high amount of psychoactive substances. The most active ingredient is tetrahydrocannabinol (THC), although more than 20 other constituents have been identified. The other ingredients of the plant resemble those of tobacco leaves [1].

The main routes of consumption of cannabis products are smoking and eating. The minimum effective dose of THC is 2 mg. If cannabis is taken orally a five fold higher dose is needed to have similar effects, predominantly due to a first-pass effect in the liver [1].

The in-competition use of cannabinoids is prohibited in sports by the World Anti-Doping Agency (WADA) [2] when the urinary concentration of 11-nor-Δ9-tetrahydrocannabinol 9 carboxylic acid, the major urinary metabolite of tetrahydrocannabinol (THC), exceeds 15 ng/ml [3].

B. The Prevalence of Cannabis in Sport

DoCoLab of the Ghent University in Belgium is the laboratory with the longest tradition in doping controls, starting in the sixties in horse doping and since 1973 also in human doping control. DoCoLab is one of the 34 laboratories world-wide that are accredited by the World Anti-Doping Agency and in 2005, 51 out of 5378 samples tested at DoCoLab tested positive for cannabinoids (0.95 %).

World-wide, 183,370 samples were analyzed in WADA-accredited laboratories in 2005. This led to 503 adverse analytical findings for cannabinoids (0.27 %) [4]. An overview on the prevalence of adverse analytical findings at DoCoLab and world-wide for the period 1998-2005 is given in Fig. 1. From these results it is clear that there is a statistically higher prevalence of adverse analytical findings at DoCoLab compared to the mean of all laboratories. Indeed, although DoCoLab only analysed ca. 3% of all samples, it is responsible for more than 10% of all cannabis cases. Moreover, in 2005, cannabis was the fourth most
detected substance in doping control laboratories world-wide and accounted for 11.8% of all adverse analytical findings [4].

Figure 1. Prevalence (%) of positive samples for cannabis at DoCoLab and in all laboratories accredited by the International Olympic Committee (IOC) or World Anti-Doping Agency (WADA) world-wide

Since there is a threshold level of 15 ng/ml for the main metabolite of cannabis and all laboratories included in this statistics are accredited by the World Anti-Doping Agency and ISO17025 guidelines, this deviation can not be caused by the individual performance of our lab. Indeed, three factors play an important role in the high percentage of cannabis positives in DoCoLab. Firstly, the fact that cannabis is only prohibited in-competition and while on an average only 1 out of 2 samples world-wide is an in competition sample, this percentage is approximately 90 percent in our laboratory. Secondly, the samples collected by the Flemish and French Community of Belgium are deriving from low level as well as top level competitions, while many national doping organisations and federations primarily focus on top level athletes. Lastly, the fact that the samples analyzed in our lab are predominantly originating from Belgium and the Netherlands, two countries that are characterized by a society and legislation which are very tolerant towards the use of cannabis.
C Rationale for Prohibition

Cannabinoids are prohibited for three reasons:

1. performance enhancement,
2. health risks and
3. the detrimental effects of cannabis use to the image of sports.

D Performance Enhancement

Generally, performance enhancement is associated with stimulating or growth promoting properties of a substance. However, performance enhancement is not only restricted to changes in physical capabilities. Psychological effects should also be taken into account.

Cannabinoids can be useful to relax, e.g. the night before a competition and a good nights’ rest will be beneficial at an event [55]. Cannabis can reduce the effects of anxiety. In certain sports, beta-blockers are also prohibited for this performance enhancing effect. Increased confidence [6] is associated with cannabis use and for high level athletes' psychology can play a role in making great achievements.

For sports where fear might influence the outcome, cannabis might reduce these feelings [7] and allow the athlete to take greater risks. This can become especially beneficial in high risk sports (e.g. snowboarding, down hill moutainbiking or bob sleighing).

E Image of Sports

Elite-level athletes serve as a role model in today's society. Although in Europe, most people do not really object to personal use of cannabis in a restricted environment, even the most liberal minds do agree that smoking cannabis should not be promoted [8,9].

Today's society does not even like famous athletes to use other, socially more accepted drugs including alcohol and nicotine. This attitude has led to a European ban on advertisements for tobacco products for sponsors of sport events or teams [10], while in the fifties some brands even stated that they sold the cigarettes for the "true" athlete.
Taking into account that children are a particularly vulnerable group for imitating habits of their favourite sportsmen several sports federations have taken steps in order to dissuade athletes from using cannabis, by putting it on the list.

**F Health Risks**

Acute health risks for cannabis users are fairly small and therefore, it can be perceived that cannabis use is not harmful. Indeed, cannabis has very low toxicity, in the sense that there are no reports of deaths caused exclusively by cannabis [1]. Nevertheless, several types of health risks can be distinguished:

*Involvement in (traffic) accidents*

Numerous studies have been performed to assess the effects of cannabis use on driving and flying skills [1,11,12]. It can now be concluded above any reasonable doubt that the use of cannabis leads to a clear but modest impairment of these skills and evidence exists that use of cannabis in combination with alcohol or other drugs aggravates these effects greatly. It is extremely worrisome that in most cases the test subjects were unaware of this reduction in skills [1]. These experiments have also shown that there was a significant decrease in attention and in the ability to react to sudden unexpected emergencies and several studies have shown that the use of cannabis leads to a distortion of spatial perception and speed [1,11,12]. Such a distortion can be dangerous in contact sports and in sports where physical contacts are possible. One could imagine for example the effects of a distorted perception of speed and distance on a tackle in soccer. Within the framework of doping control, it is also clear that smoking cannabis by for example a rally driver could have detrimental effects for a great number of persons, including the athlete himself, his co-pilot and fans along the itinerary. Population statistics of injured people after traffic accidents seem to confirm the results of the mentioned experiments. It should however be noted that in these population studies several other co-factors are involved, including the use of alcohol and other drugs. These co-factors make it difficult to attribute the increased risk for traffic accidents solely to the exclusive use of cannabis [11].

*Respiratory diseases*

It has been clearly and unequivocally demonstrated that cannabis produces chronic inflammation of the respiratory tract in regular users [1,11,13]. This
effect is manifested as chronic cough, wheezing and phlegm. Recently severe indications have also been found that regular use of cannabis can lead to the development of chronic obstructive pulmonary disease although no conclusive evidence is available so far, since in the population studies most of the subjects used tobacco concurrently with cannabis [1313].

It is estimated that smoking a cannabis cigarette leads to a threefold increase of inhaled tar as compared to smoking a tobacco cigarette, predominantly due to the way a cannabis cigarette is smoked, namely with a deep and prolonged inhalation and without a filter [1, 13]. Moreover tar from a cannabis cigarette contains higher concentrations of benzantracenes and benzypyrenes than tobacco and both substances are well known tumour promoters and carcinogens [1, 1313].

**Mental health and brain effects**

Several effects on the brain and mental health of cannabis users have been described in literature. The acute responses such as panic, anxiety, depression or psychosis that can be associated with the use of cannabis are generally quite rare and are associated with an excess consumption of the drug. Therefore, according to Johns, they might be classified as toxic effects [14]. Other temporal toxic effects described in literature are confusion and disorientation. Unless the user has a history of psychiatric problems, these symptoms only last for a maximum of a few days [11,14,15,16].

Besides the toxic short duration effects, cannabis use can also lead to the precipitation of clinically overt schizophrenia or to the relapse of previously well compensated schizophrenics [14,15,16]. Indeed, several studies have confirmed these negative effects on the clinical course of schizophrenia and it seems that besides the frequency of use and the average dose, also the age at which the use of cannabis started is a critical factor. These studies have shown a far greater incidence in the development of schizophrenia in people that started the use before the age of 18 years [11,14,15,16].

Cannabis also affects the progression of schizophrenic psychoses and worsens the prognosis. Recently, a large-scale study in New-Zealand has shown that there is a serious link between the risks for depression and suicide attempts when cannabis is frequently used [17].

An American study even provided evidence that there was a positive correlation between the increase in use of cannabis and the level of depression [18]. Nevertheless, data on this subject is still relatively scarce and several more
longitudinal studies with standardized questions will be needed before drawing definitive conclusions [1111].

Until the mid-seventies it was believed that cannabis use did not lead to tolerance and that there were no withdrawal effects, but these views have changed and indeed it has been proved that after regular use, the dose of cannabis needs to be increased to experience similar effects. Withdrawal effects are generally observed during the first week of abstinence and lead to behavioural effects as well as insomnia and increased appetite. As an effect of dependency, the need to purchase and use cannabis can lead to criminal behaviour like theft [11].

Other health effects

Nevertheless, one of the well-known acute effects of cannabis is an increase in heart rate and in blood pressure. This results in an increase of workload for the heart and in oxygen demand. Hence, if there is already a pre-existing disease that impairs the heart muscle function, the additional use of cannabis can have fatal consequences [1, 11].

Several cases have been reported of transient cerebral attacks in heavy users after smoking cannabis. These cerebral attacks are recognized precursors of strokes. It should however be noted that these attacks probably would not have occurred in the absence of pre-existing obstructive disease of the cerebral arteries [19].

Although the clinical significance is not clear so far, it should be noted that cannabis also has immunosuppressant and endocrine effects. Chronic use of cannabis appears to generate reproductive risks both to the mother during pregnancy and birth, as well as to the foetus [1].

G General Remark

Finally, following observations and concerns should be mentioned:

- It seems indeed that the acute health side-effects of cannabis are minimal, however only a few studies have been performed so far on the long term health risks of chronic cannabis use.

- Much of the work on the health effects of cannabis so far has been done during the seventies or with relatively low doses of cannabis. Indeed, the quality of the cannabis products, to use the terminology of the consumers, or
the quantity of tetrahydrocannabinol, in scientific terms, has increased tremendously over the last decades [20].

This should be taken into account when assessing risks and effects.

References


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5 THE KNOWLEDGE OF DIFFERENT TARGET GROUPS IN THE FIGHT AGAINST DOPING

Christiane Peters

A Introduction

The public’s impression of the prevalence of doping in sports is mainly based on the attention paid to individual cases by the media. The image an elite athlete projects may be very powerful, yet he probably only belongs to what is the most visible group of performance enhancing drug abusers. The larger group of so-called “sportsmen” consists of individuals doing lower-level recreational sports, who have other reasons for using drugs, mostly to improve their physical appearance [1]. In addition to the statistical analysis of all doping samples worldwide [2], results from scientific surveys confirm a high amount of drug abuse in competition as well as in recreational and fitness sports [3-5]. Furthermore, performance enhancing drug abuse is not just a problem in sports; lifestyle drug abuse as well as using drugs with the intention of improving one’s performance at one’s occupation [6] makes this matter into a new public health problem worldwide [7].

While performance enhancing drug abuse in sport is clearly defined by the list of prohibited substances and methods, and the procedures for doping controls as well as analytical methods have been prescribed in detail [8], comparatively speaking, doping prevention is as yet poorly defined. Up to now it has been regarded as a small negligible sector in the fight against doping, mainly consisting of controls and punishment.

In our highly competitive society, performance enhancing drug abuse can be observed in a large number of persons, not solely among those participating in sport activities. Therefore, the fight against doping must focus on individual responsibility and prevention [9]. The word prevention has its roots in the Latin word ‘praeventum’, and means taking all measures which shall hinder the occurrence of aberrant and conspicuous acts in terms of prophylaxis [10]. To be effective, doping prevention should therefore be about primary prevention with the aim of reducing the present risk factors and building up resources for doping-free sport before sportspersons actually get involved with drugs [11]. The main aim of doping prevention is the reduction and control of doping offences to create drug-free sport. This could be achieved by influencing the individuals themselves and their environment [11]. Therefore, the measures used for prevention should mainly support the individual’s competence to make an adequate analysis of the demands made by the social environment.
B  The Importance of the Sporting Environment

The most important points in the fight against doping are measures such as supplying information, education and bringing about changes in the individual’s consciousness. But these measures can only be effective if they take the main motives for performance enhancing drug abuse in sport into consideration. With regard to the sporting orientation, the motives can be very different indeed. While bodybuilders wish to have lean mass and less fat, weightlifters want to lift the maximum amount of weight, whereas runners, for example, want to be the fastest or to carry out long-duration workouts without a physical breakdown [1,4]. In addition, the main motives for doping misuse among Germany’s elite athletes are sporting success and financial aspects [12]. The top priorities among male pupils at school, however, are generally to become more attractive physically, to develop larger muscles or to enhance their performance in sport, while some pupils point out that it is fun to try drugs or maintain their friends do so [13]. Therefore, Laure [3] divided the motives for doping into two categories: physiological considerations, such as reducing fatigue and compensating lack of training, and psycho-social factors including e.g. economic factors, the influence of the mass media and the desire for social recognition.

Although the motives for performance enhancing drug abuse may be heterogeneous in different abuser groups, the athletes, the sporting environment and the general public are fully aware of the importance of the doping problem and the potential health risks. Public awareness of performance enhancing drug abuse was confirmed by a Swiss telephone survey, in which interviewees perceived doping as a serious problem for elite and recreational sports [14]. Furthermore, three out of four German elite athletes stated they had already thought about the doping problem in general [15]. When questioned, most of them replied they would discuss a possible abuse of doping substances with the coach, indicating that coaches are regarded as pivotal, reliable persons in the athletes’ sporting environment. Additionally, the team doctor is a very popular source of advice, if information on a substance or product is required [16]. This reveals that the physician plays a key role, being the person athletes may turn to for reliable, objective information when contemplating doping [17]. But also parents, team members, partners or friends may be involved in discussions about doping due to the bond of trust [15]. Therefore, for the success of doping prevention measures, it is important not only to focus on the individual responsibility of the athlete but also to generate positive modes of behaviour and attitudes. The sporting and social environment including coaches, physicians, therapists, parents as well as the sports clubs and schools should be involved in implementing educational programs. Because people who
use doping substances may also use recreational drugs for a non-recreational purpose [18], one has to keep in mind that drug abuse prevention programs among adolescent athletes cannot solely be limited to the list of banned substances and methods, but must include all other unhealthy forms of behaviour like smoking.

C The Athlete

Many athletes believe that banned substances and methods have performance enhancing effects [19,20]. Forbidden use of drugs implies that the drug enhances performance, which is not necessarily the case [21]. In sporting circles there is insufficient information concerning the effects of the banned substances on exercise performance, and many athletes are unaware, that some of the banned substances lack any performance enhancing effect [22].

Knowledge about the potential health risks of performance enhancing substances as well as information concerning permitted medicines in case of illness seems to be a very important factor when dealing with the doping problem. General knowledge scores about doping in general are low [23, 24] and the potential health risk associated with performance enhancing drug abuse is frequently underestimated: Of 1459 French high school students interviewed, 7% were of the opinion that doping is not always dangerous for the human body and 27% stated that doping prescribed by a physician could be used without any health risk [19]. Furthermore, boys seemed to be more careless than girls. In addition, those subjects who regarded doping as a minor health risk seemed to be more often associated with drug abusers than those regarding doping as a significant health risk [20]. In contrast, many top-level athletes used only those medicines containing no IOC banned sympathomimetic drugs, in case of upper respiratory tract infections. Those athletes competing at the higher level of sport were found to be the most knowledgeable in terms of banned over-the-counter medicines and were most in favour of their prohibition [25].

Although the prevalence of doping seems to be around 3-5% in children and may be estimated at 5-15% among adults, whatever the age, the prevalence of performance enhancing drug abuse is always higher in men than in women [3]. According to a telephone survey of pharmacists and general practitioners in Switzerland, requests for testosterone and peptide hormones were predominantly made by 20 to 40-year-old men, who were either top athletes or body-builders [26,27]. Stimulants and anabolic steroids seem to be the most frequently used drugs, followed by narcotics (cocaine, marijuana) and analgesics. Anabolic androgenic steroids were often abused in team sports like

Knowledge of Different Target Groups 233
football, baseball, basketball and rugby as well as in athletics or swimming, with the highest prevalence in weight-lifting and body-building [3]. Actual findings made by Alaranta and co-workers [20] indicate that the risk of performance enhancing drugs being used appears to be highest in speed and power sports and lowest in motor-skills sports.

Furthermore, many athletes may attempt to gain a performance advantage with the use of a variety of dietary supplements [28] in order to compensate for any exercise dependent higher consumption of energy, and mineral requirements. For athletes competing in an event this includes the risk of taking contaminated supplements on the one hand. On the other hand it may reduce the individual inhibition threshold to taking substances like pills, capsules and powders rather than a balanced nutrition, so as to be prepared for any exercise-induced demands of the human body [29]. Moreover, it has been pointed out that there are some athletes in top level sport who personally know others who use banned substances [20]. For those athletes it becomes more difficult to believe in sports ethics, being aware of the disadvantage in competition, so sometimes it may be hard to keep steadfast and continue to refuse doping.

Although distribution of performance enhancing substances in sport is prohibited, according to athletes, the three main networks for the sources of supply are [6,19,30]:

- the medical sector including a doctor, mostly a general practitioner or a pharmacist with a medical prescription,
- the black market, mostly for narcotics such as cannabis or cocaine (from traditional dealer sources) and other substances available on prescription only,
- their own social network including other participants, but mainly friends, a coach, other team members, or relatives.

This has been confirmed by Striegel and co-workers for the fitness sector, where the health care system supplies each second anabolic ergogenic substance user with their substances, frequently monitored by a physician [31]. Health reasons and the possible biomedical side effects of doping are mentioned in the first place by those athletes refusing to use doping [15].

Most of the athletes do not generally show any active personal engagement in order to get information about how to prevent doping, but get passive information from others (Peters et al., unpublished data). For doping-sensitive topics, the first contact person for athletes is the coach. The rising generation of German elite athletes frequently confers with the coach when thinking about
doping. Three out of four athletes confirmed that they had already thought about doping in general and half of them confirmed that doping associated topics, like general information about the list of prohibited substances and methods, doping controls etc. were discussed during team courses [15]. This corresponds with results from a UK survey in which elite athletes confirmed that they had received a doping educational update within the previous 6 months, but they would like to get reminders more often [16]. Education in this field requires the coach to be well informed about doping related issues, including health risks, so as to be an adequate adviser, giving knowledgeable answers on all doping related questions. A presentation of his anti-doping views, with adequate alternatives for healthy and balanced nutrition in combination with a harmonized training program, would give him the opportunity to influence his athletes in many respects, including their doping mentality.

From the athletes’ point of view, improved detection methods would be the best way to fight against doping. Furthermore, the anti-doping policy should include more supervision. While all athletes demanded severe punishments, significantly more female athletes recommended better education about health risks than male athletes [12].

D The Coach

One of the most important figures in an athlete’s environment is the coach. He plays a significant role as model, especially for young people. Many athletes accept his ideas, attitudes and ideals and grant everything he says great importance. His influence increases when training becomes more intensive and takes up more time. In exceptional cases, the coach becomes a kind of substitute parent, who is frequently consulted on private matters. This occurs more frequently among girls and women [11,32].

On the one hand the coach must aim for the maximum performance in sport; on the other hand he has to take care of the personality development of his protégés and should exemplify ethical principles [11]. The coach’s work can be very good, but only if the athlete is successful, will the output of his coaching become visible [33]. Therefore, the success of an athlete is just as important for the coach as it is for the athlete himself, sometimes even of existential, occupational relevance.

The question whether a coach is able to transmit his attitude on doping to his protégés was confirmed by an American survey done among football players 10 years ago, where a great number of athletes agreed that they would get in
trouble with the coach if they were taken by surprise when using anabolic steroids [34].

Many coaches take a doubtful look at the performance development in some special top level sport disciplines. The majority of French coaches, when replying to a written survey, considered the improvement of numerous records only possible with the support of performance enhancing drugs. Despite clearly negative attitudes towards doping, one third of the coaches responded to believe that athletes who object to doping would not be successful [35]. Therefore, many coaches would like to have doping controls amplified in the athletes’ environment [36].

In their daily work, coaches are frequently forced to give some thought to doping issues. In addition to the health related aspects, doping controls as well as the question of fairness in sport appear to be the front issues (Peters et al., unpublished data). Furthermore, doping related issues have been discussed between athletes and coaches much more often in the last few years. While in a French survey one out of six coaches stated that he had been confronted by a request concerning information about doping related issues during the previous 12 months [35], in a German survey every second coach confirmed he had been asked regularly for advice with regard to doping and doping prevention (Peters et al., unpublished data). In both surveys the coaches were asked about their attitudes and their opinion on the use of performance enhancing drugs. Additionally, information about the list of prohibited substances and methods as well as doping control procedures or health hazards were topics of conversation. During such discussions, most of the coaches did not feel educated enough for this task (Peters et al., unpublished data). More than 80% of the interviewed French coaches consider themselves badly trained for coping with the prevention of doping and less than 50% had a copy of the actual list of prohibited substances and methods or knew the World Anti-Doping Code [35, Peters et al., unpublished data].

Despite their lack of knowledge, only a few coaches actively seek more information. Yet the majority want to get it from their respective associations. Furthermore, they are interested in taking part in special educational programs (Peters et al., unpublished data). In contrast, personal engagement in support of others actively fighting against doping was poor. Only one out of ten coaches organized special measures for doping prevention or took part in such [35]. On the one hand, a possible explanation for this lack of engagement may be the feeling of not being properly prepared for this duty, although they assume they have a high influence on the athletes they coach. On the other hand, one has to keep in mind that coaches themselves confirmed having taken performance
enhancing drugs during the previous 12 months or during their sports career [35]. Therefore, a strong anti-doping policy on the part of the sports association and the national government would seem to be very important.

In order to use the coaches' support on doping prevention more efficiently in future, it would be necessary to increase their knowledge on doping problems, then they would be able to influence their athletes positively on the matter. From to the coaches' point of view, doping prevention should start at the age of 10 to 15 (Peters et al., unpublished data). Therefore, it would be important to start educational programs, not only for those coaches working in elite sports, but also for coaches working at a lower level of education, because they are in close contact with younger athletes and would be in a position to develop an anti-doping attitude among them.

E The Sports Physician

Due to their field of expertise, physicians, especially those with an additional training in sports medicine, are persons of trust regarding health specific issues and are frequently contacted by both elite and recreational athletes. While only one in four German elite athletes stated that in a case of performance enhancing drug abuse they would contact their general practitioner, every second athlete would consult a sports physician [15]. In their daily work a lot of sports physicians are responsive to doping issues put to them by athletes, mostly in search of information and education [29,30,37-40]. Most demands concern nutritional supplements and if certain medicines conform to the list of prohibited substances and methods. But in some cases questions concerning performance enhancement and biomedical side effects were also asked [40]. Other physicians confirmed that they were contacted as a source of supply for prohibited supplements [26,29,40,41] and according to some athletes, the physician in some individual cases knowingly prescribed prohibited substances during routine consultation [30].

Due to their relationship of trust to athletes and patients, sports physicians are frequently confronted with doping issues. Therefore, they would be in a position to play a decisive role in doping prevention, but they do not feel informed enough for this task. Results from an English survey of 400 general practitioners showed that only one in three practitioners knew that the doping regulations can be found in the British National Formulary. Furthermore, 12% of the responding practitioners believed that they were allowed to prescribe steroids for non-medical reasons [41].
Many practitioners do not feel well prepared for an active role in the fight against doping. In a survey done in the Netherlands, more than 70% of the interviewed general practitioners indicated the need to improve their knowledge concerning doping related issues, because they were not familiar with the substances prohibited in sports and their respective health side effects [38]. Poor knowledge about doping related issues was confirmed by French, British and German physicians [40-42], indicating that the doping prevention policy should be improved in several countries. Some authors noticed a difference in knowledge between general practitioners and sports physicians: While sports physicians working actively in the consultation and treatment of athletes deemed their doping related knowledge mostly as “good” or “very good”, only 15 - 25% of the general practitioners confirmed this statement. Therefore, nearly all sports physicians feel themselves able to give competent answers to doping related questions. But more than every second general practitioner had to deny this [40]. This stands in contrast to results obtained in a study of the Senegalese Association of Sports Medicine, where only 18% knew the definition of doping and only 15% could cite any class of doping products [39]. Nevertheless, all practitioners, whether active or non-active in the field of sport, would like to get more education concerning doping related issues [26,40].

There is a great uncertainty concerning the use of medicine in sport because of changes in the list of prohibited substances and methods and the complexity of the anti-doping policy [43].

In the sporting environment of recreational and elite athletes, the sports physician is an important member of the team. Because of his close contact to the athletes, a sports physician well informed on doping prevention would be in a good position to support the fight against doping. But a lot of them neither received any detailed information about doping during their course of studies, nor during their course in sports and exercise medicine. Therefore, they feel they have not enough knowledge and do not feel well enough prepared to take an active part in doping prevention. In addition, they fear being used as a source of supply for prohibited substances with or without their own awareness. Furthermore, unwilling to violate laws but under the obligation to take care of their patient’s health, a physician may at times get into moral conflict when supervising athletes who medicate themselves [44]. Therefore, they should have so much detailed knowledge of these problems, that the athletes who contact them may be properly informed about potential risks and about the fact that for the majority of people, proper advice on training and diet will bring the desired effect in physical performance without any need of doping substances. And finally, sufficient information about performance enhancing drug abuse
might act as a kind of protection for the physicians themselves, to prevent their being utilized unawareness as a source of supply.

F The Athletes´ Environment

To be effective, doping prevention measures should not only focus on athletes, coaches and physicians but also on the sporting environment. Therefore, the European Convention against Doping ascribed importance to the athlete's environment. The involvement of the sporting (coach, carer, club members), the social (friends, family, etc.) and the medical environment (general practitioner, masseur, physiotherapist, etc.) of young and ambitious athletes in active doping prevention would assume an anti-doping attitude on their part as well as some doping related knowledge about potential effects and health risks among the target group.

For young people who are members of a peer group, it is important to be educated within the respective social environment, because the motivation to use performance enhancing drugs may arise under peer-group pressure, with the desire for social recognition, or to feel “cool”, or because friends do so [13]. This implies, that doping prevention measures for young people should not be organised on an individual basis but in the peer-groups, clubs, teams or grades of schools to make sure that all members of the group are involved, that they all get the information about the possible health risks and receive information about alternatives for diet and training, so as to achieve performance enhancement naturally. Otherwise it could be very difficult if one individual demonstrated an anti-doping attitude contrary to that of the others in the group.

G Prevention Campaigns

In the fight against doping, it is the responsibility of the scientific community to spread scientific knowledge and to take part in the education of athletes, coaches and others involved in sports [22]. Because some older training programs seemed to be inefficient [42], special anti-doping prevention programs should be developed.

An easy and frequently used alternative source of information concerning any detail on doping or on doping in general is the internet. The National Anti-Doping Agencies of several countries as well as the websites of different sports are offering a lot of general information. However, these websites should not only provide the list of prohibited substances and methods, but also regularly
update lists of acceptable medicines as well as recommendations on healthy nutrition and efficient training. Access to the internet in addition to promotion of specially prepared websites could be a good method of improving general knowledge, but this in itself is also too limited. What happens if there are any individual questions [16]? For those people looking for objective information an anti-doping hotline could be an easy and anonymous way to get information on detailed questions. Sweden’s anonymous Anti-Doping Hotline, where 3,500 callers per year searched for information concerning doping showed that such a service would actually be used. While most callers were non-abusers, 17% stated they had had doping experience. Men called more frequently than women, with the dominant group aged between 17 and 30. Commonly asked questions were, firstly, on specific drugs and, secondly, regarding information about doping in general [7].

In contrast to these singular contact measures, complex educational programs can be carried out for several weeks: Within the American anti-doping programs ATHENA and ATLAS, young female and male students were taught about the consequences of using substances and other unhealthy behaviour, and the beneficial effects of appropriate sport nutrition and effective exercise training. Courses were organised in weekly sessions, with small learning squads under a squad leader over a period of several weeks. The programs were accompanied by special teaching material in terms of guides on sport nutrition and training. The efficacy of both programs was evaluated by a control protocol using confidential questionnaires prior to and following the sport season, indicating enhanced healthy behaviour and including less new use of performance enhancing substances, and among the girls less ongoing and new abuse of diet pills in the experimental group. Furthermore, positive changes were observed in other non-sport related but health-harming actions, for example less driving with an alcohol-consuming driver, or illicit use of marijuana and other drugs [45-47]. Similar results were obtained in a controlled French study, where a specific educational intervention showed a reduction in the intent to abuse drugs among adolescent top-class athletes [48] and in a controlled American 10-week study with student athletes, where participating athletes confirmed that drug education can be effective in preventing drug abuse [49].

**H Conclusion**

Most of the older concepts on doping prevention measures are generally used keeping the negative consequences of drug abuse in mind and are based on
the deterrent factor. Concluding from the athletes’ statements, this however did not prevent the use of prohibited substances [15].

Some newer concepts make us hopeful that prevention programs can be effective in the fight against doping and social drug abuse, but they have to be carried out in a wide area and implemented within existing structures such as schools, clubs or sport associations, to make sure that each adolescent will be involved automatically in such programs. Therefore, programs like those described in the available literature would not only require excellent concepts and clear, organisational structures but also teaching material, educated personnel, time and money in order to be carried through effectively in future.

To be effective, doping prevention measures must not only focus on athletes but must involve their sporting, social and medical environment.

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6 DOPING IN HANDICAPPED SPORT

Christiane Peters

A Historical Overview

Due to professionalizing of training and coaching in sport for athletes with a disability as well as high technical development of sport equipment exercise performance rapidly increased over the last years. In parallel, rising attention of mass media during international events like the Paralympic Games draws successful athletes into the focus of the public. Therefore, the uncompromising will to win combined with a possible financial incentive and social approval may be reasons for a considerable increase of doping in sport for the disabled.

Although negative-tested urine samples for doping analysis were taken for the first time in 1984 during Paralympic wheelchair events in Stoke Mandeville, official doping controls were started 1988 in Seoul/Korea during the Summer Paralympic Games and 1992 in Tignes-Albertville/France during the Winter Paralympic Games [1].

The continuously increasing number of doping controls reached an amount of 643 in the Sydney-Games 2000, when the first tests were found to be positive according to the World Anti Doping Code. From the 14 positive-tested urine samples three contained documented substances with medical justification. Ten of the remaining eleven official doping offences were found in power lifting, and one in athletics. Nine of the power lifters were convicted by the use of training controls. The tenth power lifter as well as the short distance runner have been under the group of medallists of their finals, but were found to be positive after their obligatory in-competition controls. On the one hand they had to return medals to the International Paralympic Committee; on the other hand, all convicted athletes received the obligatory suspension. The first positive doping control during Paralympic Winter Games was found in Salt Lake City 2002, where the anabolic steroid Methenolone was detected in the urine sample of an athlete with an amputation of the upper extremity in Nordic skiing. At International Championships of different Sports Federations or at Paralympic Games several doping controls of athletes with a disability were found to be positive during the 21st century. Due to repeated doping offence three power lifters were suspended for lifetime since the Paralympic Games 2004 in Athens.

Because performance determining factors in sport are mostly independent of a disability, in general, the kinds of sport or sports disciplines as well as the abused substances were comparable to those found in sport for athletes without
a disability. Therefore, most of the substances detected in urine samples were anabolic steroids, less frequently stimulants, glucocorticosteroids or diuretics. These substances have the same potential to induce the already known biomedical side effects in athletes with a disability in comparison to those athletes without. Therefore, in the fight against doping in sport for athletes with a disability and in conformity with the general principles of the World Anti-Doping Code the IPC Anti-Doping Code was established in 2004 with the main aim to preserve the spirit of fair play in sport for athletes with a disability.

But in comparison to non-handicapped adult persons two additional facts have to be kept in mind: On the one hand there are some disabilities, whereby athletes become reliant on guides or carers such as visually impaired athletes. This dependency in activities of everyday life including nutritional intake may bear an increased risk of becoming a doping victim due to contaminated food provided, for example, by rivalling athletes or teams. Furthermore, special attention must be given to the procedure of taking urine samples, which e.g. can not be controlled by blind athletes. On the other hand a significant number of athletes with a disability, competing in top-level sport, need to take some kind of medication. Under these circumstances additional doping may bear an increased health risk due to the combination of several medications for a special disability with regard to possible multiplying effects.

Nowadays, in-competition controls are the norm during International Championships and Paralympic Games, while out-of competition controls just take place on the verge of International competitions, indicating that a close control network is not a rule in top-level sport for the disabled. Beyond the handicap-specific problems in doping prevention and sampling of doping controls there is a risk of doping related health side effects in sports for this athletes. In addition to the potential health risks and hazards, already mentioned in literature regarding the able-bodies athletes, there are important handicap-specific aspects explained in the next chapter.

B Health Side Effects

Due to their individual disability some athletes may have conditions requiring them to take specific medications which are mentioned on the official WADA-list of prohibited substances and methods in sport. Under these special conditions they are allowed to use those substances for medical reasons but in agreement with the Anti-Doping rules they have to declare this in advance showing a therapeutic use exemption.
Beyond the well-known doping practices in top-level sport for people without a disability, there is a special doping method unique in disabled sport, which is called “boosting”. Boosting is a deliberate attempt to cause or provoke autonomic dysreflexia (AD), an abnormal sympathetic reflex which is up to an overactivity of the autonomic nervous system [2].

Because some quadriplegic athletes had noticed that the rate of perceived exertion was reduced under AD conditions and faster top speeds could be achieved in wheelchair racing, this state becomes interesting to deliberately enhance exercise performance in competitions [3]. Comments of quadriplegic athletes are e.g. “If I cannot sweat, I am not able to reach my best performance”. A significantly enhanced peak performance, higher maximal heart rate, and peak oxygen consumption were observed under experimental conditions for high level spinal cord injured athletes under AD and confirm these subjective impressions [4]. Therefore, due to the performance enhancement of AD connected with an increased health risk in spinal cord injured athletes, in 1994 the IPC deemed boosting to be a banned method [2].

AD is a state; people with a cervical or high thoracic spinal cord injury most often at or above the sixth vertebrae can suffer from. Anatomical explanation for this phenomenon is the absence of cerebral control over reflex sympathetic activity because of the transduction of the cord [3,5]. With regard to competitions in sport, it is important that persons with a high level spinal cord injury have a limited potential for improvements of the cardiopulmonary system under exercise conditions. The loss of sympathetic cardiac innervations results in a restriction of the maximum heart rate for quadriplegic and high paraplegic persons causing a limitation in the cardiac output and maximal oxygen uptake. This is accompanied by a reduced catecholamine response to exercise, and in addition, by a loss of the muscular venous pump in the lower limbs, a limitation of their performance [3].

The AD-reflex may occur spontaneously or may be provoked deliberately by distension or irritation of the urinary bladder e.g. following clamping of the urinary catheter or by distension of the bowel. Although boosting techniques do not cause any pain to athletes with paralysis, any peripheral afferent and painful stimuli to the lower part of the body may trigger AD, resulting in a rapid rise in blood pressure [3,5-7]. With regard to a generally increased risk of arterial hypertension in spinal cord injured persons, episodic increases of blood pressure following AD may additionally enhance this risk for cardiac and circulatory dysfunction [6]. Upon leg extension exercise in combination with electrical stimulation an immediate increase in systolic blood pressure was observed, giving their body a feeling of some kind of stimulation [8]. This is in
agreement with findings from others observing a lower heart rate at rest in the boosted state, as well as the ability of the athletes to achieve levels in excess of the normal maximum during exercise. In association with AD state elevated catecholamine levels were observed in quadriplegic athletes under boosting conditions, mostly due to a rise in norepinephrine, while peak lactate at the point of exhaustion was comparable with and without AD [4,5,6,9].

In addition to the blood pressure rise other symptoms like headache, sweating or gooseflesh may occur under AD. Most dangerous complications may be cardiac arrhythmia, cerebral haemorrhage, and even death [3,10]. Due to the possible health hazards AD has been regarded as a medical emergency and the IPC forbids competition in this state. Therefore, controls of the systolic blood pressure in competition for athletes with a high spinal cord injury are in progress: If in two consecutive examinations with a 10 min break it is 180 mm Hg or above, withdrawal from competition will be determined [1]. Because AD occurs spontaneously in people with a high level spinal cord injury, it is nearly impossible to catch an athlete provoking this reflex deliberately. Therefore, withdrawal of an athlete in an AD state is comparable to the protective suspension of health reasons in cross-country skiing for the able-bodied athletes.

Spinal cord injured persons have trophic, vascular and neurogene particularities, which may predispose the development of thromboembolic disorders [11]. Therefore, well-known doping substances and methods already abused in the able-bodied athletes to increase oxygen transport capability, like EPO or blood doping, may additionally increase the risk of circulatory disturbances in wheelchair-dependent athletes.

C Conclusions

With regard to biomedical side effects similar reactions of the able-bodied athletes to most of the abused substances and methods can be expected in athletes with a disability. But there are only few documented projects dealing with doping in sport for the disabled, mainly with regard to autonomic dysreflexia. Beyond the already described facts, further studies have to investigate whether the knowledge concerning health side effects of doping in athletes without a disability can be easily transferred to those with a disability or whether the dimensions of health hazards are different.
D References


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7 PREVENTION STRATEGIES

7.1 OVERVIEW ABOUT THE ACTUAL STATUS QUO IN EUROPE

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A Introduction

One of the main subjects of any health system is prevention. Unfortunately in the fight against doping activities are focused on the development of new techniques for drug identification and controls and less in prevention. Anti-doping controls must be considered as a way to guarantee a competition free of drugs and prohibited methods. But the better way to beat doping is through education, information and with the correct medical assistance. Usually most of the efforts try to discover the culprits, while other actions are neglected. Sportspeople are encouraged to win at any price while the prestige of the team, school, locality, nation they represent are at stake. On the other hand we forget that the problem is bigger at amateur or recreational levels, where most of the users are not checked medically and more often they resort to ergogenic drug abuse.

Not all states deal identically with the issue of doping in sport. In Europe for example, six countries pioneered in taking the legislative route to define the juridical framework of the fight against doping. Their concepts, measures and sanctions developed through the years, although some countries still present gaps concerning the topic of doping and few years ago only five countries had specific legislation on doping. As it is stated in the report “Harmonisation of Methods and Measurements in the Fight against Doping” by Merode and Schamasch [1]:

"Doping is not a concern only of high-level athletes. It affects amateurs and people who practise sport as a leisure activity. Fighting the problem effectively clearly means putting a stop to the trafficking that feeds it. It is therefore essential to develop cooperation between the sports world, on the one hand, and the judicial, police and customs authorities, on the other."

The present review tries to emphasize the differences and similarities between the strategies of prevention followed in the various countries of Europe. Therefore, a questionnaire was created inquiring the actions in the different countries in the field of doping prevention. This questionnaire was sent per mail to the anti-doping agencies of all European countries or queried by phone.
B Structure of the questionnaire

The main purpose of the survey was to evaluate the engagement of European anti-doping agencies in the realization and accomplishment of anti-doping and prevention strategies. Therefore a simple questionnaire of four pages containing four main chapters was distributed. 25 European Agencies were contacted and the total reflux was 22, which are assessed as 100% in our statistical calculations performed using SPSS (Statistical Product and Service Solutions). The questionnaire is partitioned into the main chapters: (1) Hotlines, (2) Training on doping prevention, (3) Doping prevention in schools/universities and (4) Distribution of prevention strategies.

**Chapter 1 (Hotlines) covers the following questions:**

a) Do you provide anti-doping hotlines?
b) Who is in charge of the hotlines?
c) Who is using the hotlines the most?
d) What are the main topics/questions asked?
e) What are the operating hours?
f) Are the hotlines anonymous?

**Chapter 2 (Training on doping prevention) covers the following questions:**

a) Do you offer training programs for specific target groups?
b) Which institution provides the program?
c) Who is teaching on the training program?
d) What are the topics of these programs?
e) How often does the training program take place?
f) Is there a curriculum?
g) Are there special materials for these programs?

**Chapter 3 (Doping prevention in schools/universities) covers the following questions:**

a) Do you address doping/doping prevention in schools?
b) Do you address doping/doping prevention in universities?

**Chapter 4 (Distribution of prevention strategies) covers the following questions:**

a) Do you hand out materials about doping and prevention?
b) Do you/did you publish articles in scientific newspapers, journals etc.?
C Prevention in Europe

Chapter 1: Hotlines

Only 41% of the contacted agencies operate an anti-doping hotline. In 62.5% of those cases the National Anti-Doping Agency (NADA) is in charge of the hotlines. 12.5% are controlled by the National Olympic Committee. Remarkable 25% of the hotlines are controlled by other institutions not further defined here. As expected, athletes for competitive sports are using the provided hotlines the most with 87.5% followed by physicians 62.5%, coaches 37.5% and, still remarkable, athletes for recreational sports 25.0% (Fig. 1). The main topics issued on phone are downward drugs & medications, nutritional supplements, prescription, doping testing, legal basis, side effects, prevention and finally health hazards (Fig. 2). 62.5% of the hotlines are operated 24 hours a day. 37.5% are just operated during working hours. In most cases the advices are given by physicians followed by trained personal, medical attendants and others including nurses, pharmacists and secretaries. 37.5% of the hotline operators claim to assure anonymity.

Figure 1. Do you provide any anti-doping hotlines and who is using them most?
Figure 2. What are the main topics and questions asked?

According to scandinavian models, the major aim of anti-doping hotlines is to decrease doping misuse and contemporaneously increase the knowledge and awareness of the potential health risks and overall consequences of doping by providing general information, education, development and actual research data [2]. Thereby, the information is divided into 6 following main fields of action: medical questions, prohibited substances, introduction of relevant organisations, maintain up-to-date anti-doping knowledge, preserve data anonymously, provide information about healthy ways of performance enhancement. Such an attempt to organize a hotline was firstly emerged in Sweden in 1993. This anonymous hotline was operated by trained nurses co-operating with clinical pharmacologists [2]. The success and acceptance of this service is reflected by the number of 25,835 calls within 7 years.

Chapter 2: Training on doping prevention

86.4% of the anti-doping agencies offer training programs mainly for athletes 89.5%, coaches 84.2%, physicians 73.7%, medical attendants 57.9% and more seldom for teachers 36.8% and for the open public 31.6% (Fig. 3). Happily, these programs are offered by 47.1% of the questioned agencies to an extend of approximately 12 hours and more. The NADA provide most (75%) of the training programs and that for free followed by the National Olympic Committee
(12.5%). Program executives are trained personals 75%, physicians 37.5%, medical attendants 25%, others (members of educational departments and scientific assistants) 12.5%, coaches 12.5% and teachers with 6.0% participation (Fig. 4). The main topics of the provided programs are in decrescent order nutritional supplements, doping testing, prevention, side effects, legal basis, health hazards, doping means and techniques (Fig. 5).

**Figure 3.** Do you offer training programs and for whom?

**Figure 4.** Who is teaching on the training program?
Figure 5. What are the topics of the training programs?

The training programs are provided by the agencies once a year (33.3%), twice a year (20%) and surprisingly also more than twice a year (26.7%). Other performing strategies are used by 20%. A curriculum is mandatory for 76.9% of the contacted agencies even if the curriculum is defined in a broad spectrum e.g. including (so named by the agencies)

- 6 core modules on anti-doping,
- variable, depending on target group,
- doping means & techniques, prevention, health hazards, doping testing, side effects, legal basis, nutritional supplements,
- new things in anti-doping fights,
- nutrition and doping control cheating,
- educational materials.

71.4% claim to use specific materials for their sessions like advertising anti-doping materials, lectures presented as articles in short (2 pages) or long version (5-8 pages), brochures information materials, leaflets, DVDs, video materials, websites, WADA list, anti-doping handbook (compilation of all anti-doping legal acts and rules) etc. All the mentioned specified materials were used in programs in similar parts around 5.0%.
There are a lot of different and well-designed efforts and serious attempts for the creation of doping prevention studies to fight against doping at its roots worldwide. But there is still a need to align all differently designed studies to compete doping in the same way worldwide. Besides biological and chemical methods to detect doping, evaluations and studies also focus on the prevention of illegal doping at all. One preventive laboratory method described e.g. is based on a Fourier-transform infrared spectroscopy analyzing serum extracted out of 50µl capillary blood [3]. The results of this measurement containing a wide range of biological molecules in a single microsample provides a "discriminatory biomolecular profile" so that individuals can be differentiated on the basis of their physiological status [3] and consequently reflecting doping misuse. This is the one active side of doping prevention. Another probably most important side of doping prevention is the contacting of the main clientele and also the main public including schools and universities. There are programmes accomplished by United Kingdom Sport (UK Sport) like the 100% ME education programme [4]. Other efforts are consultancy studies of the European Commission like „Fight against Doping 2000-2001“ [5]. Under the title „Aren’t we all positive?“ the KPMG - Bureau voor Economische Argumentatie (Hoofddorp, NL) provided a social and economic analysis of doping in elite sport. The analysis consisted a social science and a legal part and recommended that anti-doping policies should include legal and economic measures to counteract the economic powers active in sport [5].

Chapter 3: Doping prevention in schools / university

Approximately half of the European anti-doping agencies address the topic doping prevention in schools (45.5%) and in universities (50%) (Fig. 6). The age of the students confronted with this topic in school ranges mostly between 12-19 (80%) and more seldom at younger age. In the majority of cases this informative school courses are arranged between the teachers and the agencies and the attendance of the students is more or less obligatory.

As universities represent a diverse form of education the addressing is also partly organized different, so that 45.5% of the courses held in universities are voluntary and 36.4% are nonvoluntary (Fig. 7). The numbers of hours equally differ from 0.75 to 6 hours. The topics raised in university programs contain besides doping means & techniques (20.0%), prevention strategies (20.0%) health hazards (14.3%), doping testing (14.3%) also side effects (14.3%) and the legal basis (11.4%).
Figure 6. Do you address doping prevention in...?

Figure 7. Do you address doping prevention in universities and is it voluntary?

The US granted prevention studies ATLAS (Adolescents Training and Learning to Avoid Steroids) and ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives) present such possibilities of addressing doping prevention to students. These programs were started in 1996 and 2006 respectively and are still very effective and successful [6-9]. One of the root knowledges of such programs is the fact that in our society and preliminary in elite sports an increasing tendency can be seen to enhance performance with
the help of illegal drugs and methods. According to diverse European studies accomplished with high school students and athletes this phenomenon covers also children and youths using prohibited substances [10,11]. ATLAS´ objective was to test a educational intervention designed to reduce adolescent athletes´ intention to use anabolic androgenic steroids (AAS). This AAS prevention program enhanced healthy behaviors, reduced factors that encourage AAS use, and lowered intention to use AAS [6,7]. The ATHENA intervention is a scripted, coach-facilitated, peer teaching program, which was integrated into high school athletic programs. The ATHENA program altered the targeted risk factors and reduced ongoing and new use of diet pills and body-shaping substances [8,9]. These two programs show the importance of a structured process and a defined curriculum content. Furthermore, the program´s positive results confirm the potential to act as a vehicle to effectively prevent from health-harming behaviors.

Baron et al. [12] review impressively the spread of doping to at-risk populations and that developing education, prevention and treatment programs is the only way to prevent the spread of this doping abuse especially in groups like the youth.

Chapter 4: Distribution of prevention strategies

Most pleasant is the fact that at least 90.9% of the anti-doping agencies in Europe hand out informational materials about doping and its prevention. The doping prevention materials include brochures (36.4%), educational flyers (34.1%), DVDs (18.2%) and CDs (11.4%) (Fig. 8). Such hand-outs are inter alia advice cards on prohibited substances, testing procedure leaflets, medication database promotional cards (www.didglobal.com) and outreach for events & seminars. This listed material was equally distributed among National Federations & Sports Clubs, Health National Centres, athletes, coaches, top level/elite athletes, teachers, physicians and pharmacists. The informational material was provided on request, using media, in doping control offices, during sample collection or during competitions. Unfortunately, just 25.0% of the agencies mail actively, while 75.0% act only on demand.
Figure 8. Do you hand out materials about doping prevention and if yes, what kind of material?

The attempts towards using TV spots or radio shows for anti-doping prevention activities is marginal. Only 31.8% of the European agencies use this tool of information spreading. The major part of the agencies (68.2%) never thought about reaching the public by TV or radio. 59.1% of the national anti-doping agencies submitted scientific papers in journals or newspapers, presenting their accomplished work in the field of anti-doping prevention activities [e.g. 13-16].

D Conclusions

Differences among the anti-doping strategies exist still between the European countries, although they share the common points of prevention and suppression. The methods used to attack the problem of doping are being made progressively stricter, although this is not always well received by everyone.

Such is the case of the well-known and controversial legal establishment of official testers e.g. in France, Italy, Belgium, and Spain who can carry out their work by surprise, i.e. coming unannounced at night into sportspeople's rooms or into team facilities to determine whether there exist any doping materials. This practice have yield fruit in France and Italy during the Tour de France or the Giro d'Italia but they have also met with an indignant response from the sportspeople who feel that it is an outrage to themselves as persons, and unanimously consider that their fundamental rights have been violated.
An important preventive action would be to accomplish that all people linked actively or inactively to sports participate in the various anti-doping actions. The road to take is to alert these people to the health problems caused by doping substances. Indeed, most of the countries studied in this review now view doping in their laws and adjudications as a helping tool to arouse people on this topic. As well as health messages all European campaigns should always concomitantly aim to promote the ethical values of sport.

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7.2 **Drug Prevention and Health Promotion for High School Athletes: A Summary of the ATLAS and ATHENA Programs**

*Melissa B. Durham, Linn Goldberg*

This article summarizes the information provided at the EU Symposium in Munich, Germany regarding the need for effective drug prevention and health promotion education for adolescent athletes and descriptions of the ATLAS and ATHENA interventions, two gender-specific, evidence-based programs for adolescent athletes.

**A Background of Drug Use in Sport for Young Athletes:**

*Is there a problem?*

Alcohol and drug use is the leading cause of adolescents' injury and death in the United States [1]. Adolescent illicit drug and alcohol use has stayed relatively steady or slightly declined over the past five years, but current use among youth ages 12-17 remains high [2]. During 2004, over 30% of 10th grade students (32.8% males; 33.6% females) and approximately half of 12th grade students (50.7% males; 43.3% females) reported using alcohol [2, 3]. Over a fifth of the 10th graders (23.8% males; 20.2% females) and of the 12th grade students, 33.4% of male seniors and 22.7% of female seniors reported binge drinking, while marijuana use among 10th and 12th graders was 16.7% males, 13.4% females and 23.6% males, 15.8% females, respectively [3].

Anabolic steroid use is linked to this drug and alcohol use among adolescents. Most studies report that 3-12% of adolescent males admit to using an anabolic androgenic steroid (AAS) at some time during their life [4]. According to the United States Center for Disease Control survey in 2005, the percentage of 9th-12th grade students who took steroid pills or shots without a doctor's prescription one or more times during their life was 4.8% (+/-0.8) for males and 3.2% (+/-0.5) for females [5]. However, this study included all students, not just those participating in school sports, whose use of steroids is considered to be higher. While steroid use is relatively low compared to some of the more popular drugs, it has been a growing problem, especially among young women [6]. With approximately 19.5 million adolescents in the United States, over 1.5 million in the United States have reported using steroids in 2005 [5, 7].

In the United States, high schools have school-sponsored sports programs and more than 50% of the students participate [8]. Despite the potential health benefits from participating in athletics, adolescent athletes, especially males,
may be at higher risk than their non-athlete peers for engaging in health-harming behaviors [9, 10]. Naylor (2001) and French (1995) discovered that athletes are not protected from health-harming behaviors because of their athletic participation [11, 12]. Multiple regional and national studies by Yesalis (1993), Buckley (1988), Johnson (1989), and Johnston (1998) have reported high school athletes use some illicit drugs at the same rate or more frequently than their non-athlete peers [13, 14, 15, 16].

DuRant, Escobedo and Heath (1995) reported that adolescent athletes who use anabolic steroids for improving their athletic potential often use a variety of other illicit substances [17]. In a study among younger adolescent (6th, 7th and 8th grade students) sports participants, as compared with non-sports participants, significantly higher frequencies of weapon carrying, use of alcohol, and experimentation with tobacco was found [18]. While anabolic steroid use is more common among males, Becker (2002) and Byrne (2001) have shown that young women high school athletes use diet pills and other body shaping substances, including steroids, at higher rates than their non-athlete peers [19, 20].

B Risk Factors for Anabolic Steroid Use, other Substance Use and Disordered Eating Practices

There are associated behaviors for young steroid users that may underscore the need for the critical elements in a steroid prevention program. In a study by Bahrke, Yesalis, Kopstein, and Stephens (2000), adolescent AAS users were significantly more likely to be males and to use other illicit drugs, alcohol and tobacco [21]. Student athletes are also more likely than non-athletes to use AAS; and American style football players, wrestlers, weightlifters and bodybuilders have significantly higher prevalence rates than students not engaged in these athletic activities. Anabolic steroid using males have been found to have lower self-esteem and higher rates of depressed mood and attempted suicide, poorer knowledge and attitudes about health, greater participation in sports that emphasize weight and shape, report greater parental concern about weight, and higher rates of disordered eating and substance use [22].

Among female steroid users, a similar pattern of results emerged. Students in grades 7-12 in the state of Nebraska were assessed for their anabolic steroid use. Of the students who reported using anabolic steroids, 72.6% were sports participants. Female steroid users had a greater likelihood of using alcohol,
tobacco, and other drugs than their non-steroid using counterparts. Also, these anabolic steroid users were more likely than nonusers to report violent acts [23].

In Sweden, researchers attempted to assess the importance of risk factors such as socio-demographics, sports activities, tobacco use, alcohol consumption, use of certain psychotropic substances and violence in the use of doping agents in adolescents. Their assessment was that the use of doping agents in Sweden probably involves more than a desire to enhance appearance or sports performance and had much in common with use of alcohol, tobacco and psychotropic drugs [24].

Other adolescent drug and alcohol use is associated with the development of disordered eating practices among young women. This may be due to the finding that unhealthy behaviors have similar risk factors including, but not limited to, depression, observation of role models, concerns about body image, an emphasis of unattainable and unrealistic images of men and women in the media, and peer influences [25, 26, 27].

C Depression

Several authors have studied the relationship between depression and substance use or abuse, along with disordered eating behaviors for adolescents, but the causal pathway is unclear [28]. Alcohol use can lead to depression and depression can lead to alcohol use and disordered eating behaviors. Bukstein, Brent, and Kamainer (1989) found that the most common precursors of substance use or abuse were depression in girls and antisocial behavior in boys [29]. Khantzian (1985) discovered that adolescents who were depressed began consuming alcohol as a way to self-medicate [30], while Teri (1982) and Windle and Davies (1999) reported that adolescent females experienced higher levels of depression than did males, but for all of the depressed adolescent males and females, they engaged in heavier drinking than their non-depressed peers [31, 32]. For young women, depression appears to be a risk factor for both substance abuse and disordered eating behaviors such as vomiting and fasting [27].

Other research suggests that the earlier misuse of alcohol begins, the greater the likelihood that psychiatric problems, such as depression, will occur. Buydens-Branchey, Branchey, and Noumair (1989) report that adults who had started abusing alcohol in their teens were three times as likely to be depressed as their non-abusing peers [33]. Likewise, Koenig & Wasserman’s (1995) study
found young adolescent women to more likely become depressed if they experimented with disordered eating behaviors, such as dieting [34]:

As dieting is typically unsuccessful as a means of long-term weight control, depression will result from the sense of failure and helplessness associated with dieting failure. This depression then leads to increasingly maladaptive eating behaviors that serve to assuage negative affect and regain control over body appearance (p. 225).

D  Role Models

Role models, such as professional athletes, are also an influence on adolescents’ use of drugs and alcohol. Professional Major League Baseball players Mark McGwire and Rafael Palmeiro testified in March 2005 before the United States Congress on the issue of doping in baseball [35]. Although McGwire had previously admitted using androstenedione (a steroid precursor) before it was banned by the U.S. Food and Drug Administration, he refused to discuss any drug use during his testimony, repeatedly stating, “Like I said, I’m not here to talk about the past.” Palmeiro’s testimony included this statement, “I have never used steroids, period.” Five months later, after Palmeiro tested positive for anabolic steroids, he rephrased his prior testimony by announcing, “I have never intentionally used steroids” [35]. Their action may impact adolescent behavior because of their athletic accomplishments and monetary rewards. Some believe their steroid intake glamorizes use and promotes dishonesty [36].

Palmeiro and McGwire are not alone. Other professional athletes from different sports have denied doping allegations, but some have been discovered and in some cases, banned from competition for using steroids or tampering with their drug test. Both Michelle “Smith” de Bruin, an Irish Olympic swimmer, and Justin Gatlin, an American Olympic track athlete have been sanction for steroid use (Gatlin) and specimen manipulation (de Bruin) [37, 38]. Soon, the results of Floyd Landis’ appeal in court will assess his guilt or innocence regarding the allegation and positive test for steroid doping. Landis had elevated ratios of testosterone to epitestosterone during the 2006 Tour de France. If Landis’ appeal fails, he could be banned from cycling for two years [39].

E  Media

The media, including advertisements, covers of magazines, television, movies, websites and more, play a powerfully influential role in shaping both adolescent
attitudes towards drug and alcohol use and their beliefs about what body types are acceptable by society [36, 40]. Many companies use the phrase “on steroids” to advertise bigger or more powerful products for sale. In this respect, anabolic steroids have a positive connotation [36]. For example, the 3M Corporation advertised the Post-it Easel Pad by stating, “Think of it as a Post-it Note on Steroids” [41]. The word “steroids” is often displayed in a larger font than the brand name of the product (e.g., advertisement for Saab motor vehicles: Steroids vs. Saab). Often only the positive effects of steroids are represented in the advertisement; getting bigger, faster, and more powerful.

Adolescent viewers of this type of imbalanced media presentation do not learn that steroids are illegal, they can cause acne, shrunken testicles, baldness, stunted height, multiple health problems, or that injecting steroids increases the risk of developing AIDS [41, 42]. Imagine reading an ad for Saab engines that said “This is a Saab on heroin.” Heroin has a negative connotation in the United States and would not assist product sales; in part because of the well known side effects that include exposure to disease from needle sharing, mood disturbances, and cardiovascular problems [43].

F Body Image

Kilbourne’s (2007) work has raised awareness about the media presentation of young men and women for decades [44]. Covers of magazines often display images of men that are very muscular, lean, and handsome. Images of women, or parts of their bodies, have flawless skin, very thin physical frames with skimpy clothing, enlarged breasts and perfect teeth. The images are digitally enhanced and present an unattainable, unrealistic image to the public. Young adolescent men and women are bombarded by these images, often using them as a reference for comparison with their own bodies. Due to this exposure, males desire a larger, more muscular frame and females typically want to lose weight, purchase self-improvement products, and feel inadequate. This unnecessary pressure on adolescents to look a certain way leads to health-harming behaviors [40, 44].

G Peer Influence

Along with role models, the media and body image, the behavior and choices of an adolescent’s peers are very influential. Buddeberg-Fischer and Reel (2001) reported that adolescents are more likely to listen to their peers than any other person, including a parent, a coach, or a teacher [45]. For those who are in a
peer group that is experimenting with drugs and alcohol, they are also more likely to ride in a car with a drunk driver, wear their seatbelt less frequently, engage in sexual activity more frequently, demonstrate antisocial behavior including violent, aggressive behavior, and their academic performance is more likely to decline [9, 10]. However, peer influence can also be a protective factor. Adolescents who choose to abstain from substance use often attract friends who share similar beliefs and make healthier choices [9, 10].

H Female Athlete Triad

For young women athletes, the pressure to be thin and athletic can lead to unhealthy eating habits such as fasting, vomiting, over-exercising or use of body-shaping substances like steroids, laxatives or diet pills [46]. If left untreated, a reduced level of estrogen in the bloodstream may cause amenorrhea and weaker bones. Osteoporosis may develop from the imbalance in hormones and lack of nutrients in the woman’s diet. This cyclical effect is referred to as the Female Athlete Triad [46]. If young women practice these unhealthy behaviors, they risk developing injuries and permanent harm. Because eating behaviors and substance abuse have similar risk and protective factors, substance abuse prevention programs for young women should address unhealthy eating habits as well [10].

I Protective Factors for Preventing Substance Use

Adolescent behaviors often cluster, meaning one health-harming choice may lead or be associated with another [17]. The same may be true for positive healthy behaviors. The National Institute on Drug Abuse (2003) summarized the factors that protect adolescents from health-harming behaviors [47]. These include positive social support, healthy peer attitudes, heightened perception of risk, engaging in healthy activities, and having realistic beliefs about images in the media. For example, adolescents are more likely to remain drug free if they have a group of friends and a positive outlook on life, they believe experimentation with drugs and alcohol is risky and they can entertain themselves without it, and they are able to critically analyze what they see in the media [36, 40, 47].
J Why Programs Often Fail

Substance abuse prevention programs for adolescents are not effective at changing behavior if they only rely on adult lectures, use scare tactics or slogans, aim to be universal rather than gender-specific or only provide knowledge [48]. Adult lectures lack the important influence that peers have on one another, especially for adolescents, to improve behavior. Adolescents are in a stage of life where they feel invincible, as if they can avoid being harmed [49]. Adolescents can have difficulty imagining themselves getting older or having any type of lasting effect from their present choices. For this reason, scare tactics about drugs and alcohol and anabolic steroids are ineffective [50]. Often adolescents believe they are protected from experiencing negative side effects [48, 49).

Successful prevention programs help adolescents build their skills through practice and rehearsal [48]. For substance abuse prevention, adolescents must learn to be able to refuse an offer for drugs or stand up to their peers when they are engaging in unhealthy behaviors like excessive dieting or using diet pills. Peer pressure is intense and unfortunately, refusing unhealthy behaviors requires a more complex approach than the once used slogan in the United States, “Just Say No”. Multifaceted prevention programs are required for effective behavior change [9, 10, 48].

Adolescents prefer to talk about the changes their bodies are experiencing or decisions they are trying to make in a homogenous environment [48]. Programs that provide a comfortable environment where members of the opposite sex are not present allow adolescents to discuss their thoughts and ask questions more openly. An adolescent needs honest information about the benefits and consequences of a decision, support from peers, and an incentive to change their behavior [48]. The most successful prevention programs present balanced information, allow peers to influence and teach each other, engage people in activities, and allow adolescents to experience something new so there is an incentive to make a change [9, 10, 48].

K Two Effective Programs: ATLAS & ATHENA

ATLAS (Athletes Training & Learning to Avoid Steroids) and ATHENA (Athletes Targeting Healthy Exercise & Nutrition Alternatives) are examples of two evidence-based, gender-specific, drug prevention, and health promotion programs for adolescent athletes. They were developed and researched through two separate National Institute on Drug Abuse grants. To date, ATLAS
and ATHENA are the only substance abuse prevention programs for high school athletes recommended by the United States legislation known as the Anabolic Steroid Control Act of 2004 and signed into federal law in October 2004.

ATLAS and ATHENA incorporate the following principles of effective program delivery: they are gender-specific, integrated into high school athletic programs, rely on peer teaching and coach facilitation, are interactive and engaging, scripted to enhance fidelity, and encourage students to create their own health promoting messages, tailoring the communication to the intended audience.

L Behavioral Theories Provide Foundation for Prevention Programs

Two behavioral change theories guided the development of the ATLAS and ATHENA Programs. The Theory of Reasoned Action describes how behavior is based on beliefs, attitudes and intentions [51]. For example, an athlete will decide to use drugs if she believes that her peers are using drugs, they won’t disapprove of her for using drugs and the drugs will improve her performance. ATLAS and ATHENA change adolescents’ beliefs about societal norms; students realize fewer peers are experimenting with unhealthy behaviors than they previously thought. Together as teammates, they set goals to improve as athletes with sports nutrition and strength training rather than cheating and taking drugs. Bandura’s (1977) Social Learning Theory provided another intervention model [52]. Social learning is a process that occurs as a function of observing, retaining and replicating behavior observed in others [52]. In addition, it is based on rewards and consequences from a social group and reinforces the power of the environment in modeling behavior. A sports team presents an opportunity for teammates to observe each other, build their skills and understand the rules of engagement, learn how to achieve acceptance from teammates, and behave in a supportive way to contribute to the team’s overall goals [9, 10].

M Specific Aims

ATLAS and ATHENA encourage athletes to work together to achieve improved sports performance and health by understanding and practicing strength training techniques and sports nutrition. Participants set weekly nutrition goals and reinforce healthy behavior norms through the development and presentation of public service announcements. The curricula for ATLAS and ATHENA have unique components because males and females develop
unhealthy behaviors for different reasons. ATLAS teaches young males how to strength train and eat enough protein and calories to increase their muscle mass. ATHENA emphasizes calcium intake for bone health and the importance of eating protein to maintain and repair their muscles, but avoids discussion of calories. Carter, Stewart, Dunn, & Fairburn, (1997) found that discussion of calories by young women has been associated with the development of eating disorders [53]. For this reason, calorie counting is not emphasized in the ATHENA curriculum [10].

Because young women are at a higher risk of experiencing a low mood and depression than young males, ATHENA provides a mood diary for young women to keep track of their fun activities and observe how their mood relates to their daily activities [27]. The mood diary is modeled after Clarke’s (1995) effective depression prevention program for adolescents [54]. For young women, ATHENA emphasizes team building activities to build social support and positive attitudes. Alternatively, ATLAS addresses young males’ impulsivity in decision making. ATLAS provides a balanced presentation of the benefits and consequences associated with illicit substance use [10]. ATLAS training strengthens athletes’ refusal skills, meaning their ability to resist an offer to use drugs.

Both programs incorporate a media deconstruction activity so athletes attain a more critical view of the images to which they are exposed. Young males analyze advertisements from body-building magazines to uncover some of the side effects of steroid use. Young women analyze alcohol, tobacco, and nutrition supplement advertisements. Athletes discuss what actually occurs when you engage in substance abuse and spend time remaking an ad to create a more realistic image of the consequences of smoking, drinking or taking unregulated supplements.

Both programs were rigorously evaluated by multi-year, randomized controlled studies. The results have previously been published [9, 10]. A brief summary of the results after one year of exposure to the ATLAS or ATHENA intervention is listed below. Please refer to the publications for further explanation.
ATLAS Results

- New anabolic steroid use decreased 50%
- New alcohol and illicit drug use decreased 50%
- Occurrences of drinking and driving declined 24%
- Improved nutrition practices
- Improved strength-training skills
- Reduced use of performance-enhancing supplements
- Students believed they were better athletes

ATHENA Results

- Less use of performance enhancing substances (steroids, amphetamines, supplements)
- Less new and ongoing use of diet pills
- Improved nutrition practices
- Less riding in a car with a drinking driver
- Less new sexual activity
- Fewer injuries
- One to three years following graduation: improved nutrition and reduced use of alcohol, marijuana and diet pills

Training for Coaches or Program Instructors

The Center for Health Promotion Research (CHPR) team provides training for effective implementation of the ATLAS and ATHENA programs. Training participants learn the current trends in adolescent athlete substance abuse, underpinnings of effective drug prevention and health promotion programs, alternatives to drug use (sports nutrition and strength training) and the background and outcomes of ATLAS and ATHENA. Coaches receive practical experience learning to use the programs so they feel confident integrating the program sessions into their usual team activities. Training is accomplished in one day-long workshop. Ongoing technical assistance is available for all participants through CHPR.

Program Materials

The ATLAS and ATHENA Programs provide gender-specific content, but the information is presented in the same manner. The program materials consist of a Coach or Instructor Manual, a Squad Leader Manual, a Team Workbook and
an Athlete’s Guide. Each coach receives the Coach Manual containing background information on sports nutrition, strength training, and drugs in sport. The Coach Manual has a squad leader training guide, the curriculum sessions (10 for ATLAS, 8 for ATHENA), and extra materials for the program. Selected student-athlete leaders called Squad Leaders use their Squad Leader Manuals to lead most of the activities within their small groups. The Squad Leader Manuals have the same curriculum sessions that their coach has with the answers. This way, they are the instructors for their groups. For every five athletes, one is the designated Squad Leader. All other teammates need a Team Workbook to participate in the activities. Team Workbooks contain the curriculum sessions without the answers. All participants receive a pocket-sized Athlete’s Guide containing information about sports nutrition, healthy choices at fast food restaurants, strength training routines, drugs, vitamins, supplements, and more.

**P ATLAS & ATHENA: Beyond Research and Development**

Currently, over 30 states and Puerto Rico have high schools that have incorporated ATLAS and ATHENA within their athletic programs. Further research could verify whether ATLAS and ATHENA could be beneficial and effective for adolescent athletes within other countries and cultures outside of the USA.

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P01 Hemoglobin and hematocrit in elite athletes - cross-sectional and longitudinal aspects

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Against the background of erythropoietin-doping and its interpretation, the special interest is focused on the natural behaviour of hemoglobin (Hgb) and hematocrit (Hct) [1, 2, 3]. The Hgb and Hct values collected over 15 years from male (n=210) and female (n=84) elite athletes in track and field as well as rowing in the laboratory or in field testing will be presented in cross and 12 weeks longitudinal sections, during rest and during training. – The determination of both parameters was done in the laboratory using a semi-automatic hematology system (Sysmex F-800, DD-100, Fa. Toa, Japan) and during field testing using a Hgb photometer following the principle of the cyanhemoglobin method respectively a Hct-centrifuge. Mean values for Hgb were 16.5 ± 1.3 g/dl (max 22.2 g/dl) in males and 14.7 ± 1.1 g/dl (max 18.3 g/dl) in females. The corresponding values for Hct were 48.8±3.1 vol% (max. 60.0 vol%) and 44.6±3.3 vol% (max 59.0 vol%). Frequency distributions show that 74 % (40 %) of all Hgb values in males are >16.0 g/dl (>17g/dl) and 72 % (40 %) of all Hgb values in females are >14.0 g/dl (>15 g/dl) (2). Hct for 28 % of men is > 50 vol% and for 30 % of women is > 45 vol% (3), whereby the longitudinal variation is 5 % on average for the whole group and 8 % in individual cases; variation over the day is up to 15 %. There was no erythropoietin substitution, i.e. all of the values found resulted from environmental circumstances and training itself. The findings of this study show that a reconsideration of the respective limit values is imperative.


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**P02 Health side effects of doping substances on the immune system: the importance of study this problem.**

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Today there is still a big lack of information about the scientific knowledge of the side effects of doping in both competitive sports and recreational ones. In addition this knowledge are not always unified and in our opinion it is very important to harmonise in Europe the scientific information about the biomedical side effects of doping, in order to get chance for preventing this practise.

Most of the information about the side effects of the different doping substances is available on the respiratory and cardiovascular systems as well as the brain. However, little information is currently examined about the side effects of doping substances on the immune system. Today it is clearly known that exercise modulates the immune system, and while moderate exercise stimulates most of the immune responses, intense exercise can be dangerous for the adaptative response mechanisms. In addition, the exercise-induced changes are mediated by different hormones released during the exercise, mainly the so called “stress hormones”. Then, a modification of the neuroendocrine balance by hormones intake during the exercise practise modify the feed-back of the neuroimmune mechanisms, and may seriously affect the normal function of the immune system, damaging sportspeople’s health.

However, although there are a lot of investigation about different substances (i.e. anabolic steroids, stimulants, narcotics, diuretics, nutritional supplements…) related to doping, and about these substances on immune system at pharmacological concentration; nothing is known about the biomedical side effects of these doping substances (at raised blood concentrations) on the immune system during exercise, an special physiological situation.

The purpose of this communication is to emphasize the importance of study the biomedical side effects of doping substances on the immune system, above all during exercise practise, as well as to show the lack of information at this respect.

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P03 The alteration of the urinary steroid profile under the stress

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In the second part of twentieth century anabolic-androgenic steroids were introduced in doping practice and received continuously increasing significance. In order to prove the usage of doping substances, the determination of steroid profile in the urine came into practice. Several factors may be responsible for alterations in the normal steroid profile for example age, sex and diet.

The aim of this paper was to find out, whether the psychological stress may cause modifications in the indicators of the steroid profile.

The steroid profile was determined in the group of 34 students of pharmacy being in non-stress conditions and under stress immediately before the important university exam. The intensity of stress was rated by self-reported questionnaire. The intensity of stress feeling was taken into account. The GC/MS method was applied to determine the steroid profile in the urine samples.

The results of the experiment have shown that psychological stress may cause significant changes in the steroid profile, especially in females. Physical activity, independently of stress significantly modified the steroid profile.

The observed changes in the testosterone and epitestosterone levels did not influence the T/Et ratio. In males higher level of stress caused the decrease in the T/Et ratio (from 1.28 to 0.53). Physical activity did not change significantly steroid profile in males.

In summary, psychological stress modifies the steroid profile in females and males but the magnitude of the observed changes does not indicate the possibility of significant modification of the results during doping analysis.

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P04 Cannabinoids in polish athletes

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The main biologically active component of cannabis, tetrahydrocannabinol (THC) has sometimes been detected in athletes' urine samples that may suggest active or passive marijuana smoking. Since THC has a narcotic property, its application is forbidden also for athletes. However, cannabinoids are prohibited in sport in competition only. According to the anti-doping rules maximum acceptable level of carboxy-THC (the main THC metabolite) detected in urine athletes is equal to 15 ng/ml [1, 2].

This study on THC content in urine was performed during the years 1998 - 2004. Urine samples (n=13,631) were taking in-competition (n=8,490) and out-of-competition (n=5,141), from polish male and female athletes engaged in different disciplines of sport.

The results were presented as a percentage of samples containing cannabinoids (%THC) with respect to the appropriate subgroups. Carboxy-THC was detected in 1.95% of total samples. The percentage of cannabinoids positive samples in females (0.21%) was markedly lower than that in males (2.75%). Cannabinoids were found in 1.7% of total samples in competition and in 2.3% of those out of competition. The most frequent (2.65%) usage of THC was revealed in athletes' age from 16 to 24y.

Relatively high numbers of positive samples with cannabinoids were found in rugby (11.27%), figure skating (5.63%), boxing (4.91%), badminton (4.20%), speed skating (3.44%) and bodybuilding (3.37%). Only sports for which more than 50 samples were analyzed were taken into consideration.

In the year 2003, the percentage of samples of polish athletes found positive for cannabinoids (carboxy-THC > 15 ng/ml) was 0.79% while in the all World IOC/WADA accredited laboratories was on average 0.25%. The similar proportion was found in the next year (0.81% in Poland and 0.31% in the other laboratories). For this period from only laboratories in Gent and Paris reported higher relative number of positive cannabinoids samples than Warsaw laboratory.


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Goal-directed measures to prevent doping and drug abuse in sports require empirical data. In this connection a cross-sectional-analysis was carried out in 2004. The purpose of the study on the one hand was to register reliable data of the current situation in Thuringia, and on the other hand it was to give information on possible interventional steps with scientific support. Within three months 2319 adolescents out of 16 Thuringian schools (5 regular schools, 4 secondary schools, 3 sport schools and 4 vocational schools) were surveyed.

346 (15.1%) students out of 2287 students (26 students without a statement) indicated use of prohibited substances from the WADA - list in the previous year: 16 (0.7%) anabolic-androgenic steroids (AAS), 10 (0.4%) growth hormones, 56 (2.4%) stimulants, 305 (13.2%) cannabis, 2 (0.1%) diuretics, 52 (2.2%) cocaine/heroin and 6 (0.3%) erythropoetin. Moreover, non-athletes (N = 490) reported a substance use that was approximately 5.0% higher than that of recreational athletes (N = 1254) and nearly three times as high as that of competitive athletes (497).

All three groups (non-athletes, recreational athletes and competitive athletes) performed poorly on a knowledge test regarding doping in general with an average below 60% in each case.

Another main aspect of the study was to determine factors influencing substance use in sports. Besides the doping specific knowledge (Beta = 0.06, p < 0.05) age contributed (Beta = 0.09, p < 0.05) as well as anti-doping attitude (Beta = -0.34, p < 0.05) to the resulting variance. Gender, however, played no role.

The findings of the study point towards the need for improvement of specific knowledge of doping among students, and that their attitude towards doping must be altered. The goal in this case is to test the effectiveness of appropriate scientific intervention.

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Anabolic androgenic steroid (AAS) abuse induces unfavorable cardiovascular events and different models for these effects have been suggested (1, 2). It is still unclear to what extent apoptosis takes place in these processes. In postmitotic tissues, like myocardium, loss of myocytes would lead to functional failing and cardiac diseases (3). Bcl-2 family proteins and mitochondria play a key role in the triggering of apoptotic cascade (3, 4). A study demonstrated increased cardiomyocytes’ apoptosis after AAS treatment in vitro (5). Up to now the effects of chronic AAS administration on the cardiac apoptotic potential and heat shock protein (HSP) level have not been studied in vivo.

The aim of the study was to investigate the effects of AAS on aerobic capacity, ultrastructure, inducible HSP72 and some apoptotic proteins in rat myocardium. Male Wistar rats were divided into two groups (n=10). One group received 10 mg·kg⁻¹·wk⁻¹ nandrolone decanoate (ND) for 6 weeks and the other group - placebo (PL). At the end of the experiment submaximal running endurance (SRE) and VO₂max tests were performed for all the rats. Samples from left ventricles were taken and immunohistochemical reactions for HSP72, Bcl-2 and Bax were done, accompanied with TEM study. Protein expression was assessed by specialized software. We found no differences in SRE and VO₂max between the groups. TEM analysis demonstrated that most of the mitochondria of ND group were swelled with reduced and not well defined cristae. In comparison with the controls HSP72 immunoreactivity was decreased in ND rats (P<0.05). The expression of pro-apoptotic protein Bax was higher in the cardiomyocytes and coronary endothelium of the steroid treated rats (P<0.05). Anti-apoptotic protein Bcl-2 did not differ between groups. Bcl-2/Bax ratio was lower in ND group than that in PL rats (P<0.01).

In conclusion, supraphysiological doses of ND do not improve SRE and VO₂max but attenuate the expression of cardioprotective HSP72 and increase apoptotic tendency in myocardium of untrained rats. The disturbance of the inner mitochondrial membrane integrity and decreasing of Bcl-2/Bax ratio reveal one of the potential mechanisms through which ND treatment leads to loss of cardiomyocytes by apoptotic pathway. Reduction of contractile cells and endothelial alterations could explain some of the cardiovascular sequels of AAS abuse.


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Poster Abstracts

P07 Gross cardiac pathology in medicolegally examined deceased users of anabolic androgenic steroids

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Anabolic androgenic steroids (AAS) represent a group of compounds that have been connected with cardiac hypertrophy, arrhythmia, unfavourable blood lipid profiles and myocardial infarction. However, scientific data of increased risk for cardiac death among users of these compounds are at best questionable.

We have addressed this issue by retrospective mapping of the occurrence of diagnosed coronary sclerosis with significant stenosis and cardiac hypertrophy and by exploring the heart weights with consideration to the body weight among medico-legally examined deceased users of AAS (n=92) employing subjects without suspected abuse of AAS or illicit drugs and who died in traumatic accidents as controls (n=96). In order to control for age, comparisons the AAS users and controls were divided into two age strata; those who were 30-years-old or younger and those who were 31-years old or older. Use of AAS was associated with a high prevalence of cardiac hypertrophy in both age groups (35% and 36%, respectively) (AAS vs. contr 30-years-max: RR = 3.71, p<0.0001 and 31-years-min: RR = 2.68, p=0.06). When body weight was taken into consideration, both the AAS-users and the controls had a highly significant correlation between body weight and heart weight. At the same time there was no difference with respect to the heart weight/body weight ratio. The prevalence of coronary sclerosis was significantly higher among the younger AAS using subjects (AAS: 14 % and controls: 2%, RR=9.1, p=0.01). Among the older subjects this difference had levelled out (16% vs. 11%). Thus, it appeared as if the diagnosed cardiac hypertrophy among several AAS users could be an adaptation to the increased body weight that is a result of a generally increased muscle mass. However, the increased heart size may still be pathological considering that the increased muscle mass to a great part is dependent on long term supraphysiological levels of testosterone resembling substances. Furthermore, our results indicate that use of AAS may in deed accelerate the development of coronary sclerosis, although this effect might be confined to certain predisposed individuals.

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Poster Abstracts

P08 Scientific criteria to differentiate the nandrolone endogenous or exogenous precedence

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Nowadays the world of sports analyses has suffered a great evolution. Just like this, doping technicals and methods used for these practices have suffered the same evolution. One of the challenges, it is to be able to discern among the possible endogenous or exogenous precedence of given substances (metabolites of nandrolone) that appear in the list of products forbidden in sports. Two types of studies exist: direct evaluations ((Gas-Isotopyc relation-MS Chromatography (GC-IRMS), hair analysis)); and indirect evaluations (Hormonal valoration in serum, evaluation of the esteroideal profile difference among sulfoconjugated and glucoconjugated fractions, test of stimulation with hCG for the evaluation of a possible alteration of aromatase systems). In the case of the nandrolone and its metabolites we present the obtained data when we applied the variations of the relation Testosterone/β-Estradiol (T/βE) as scientific criteria.

We have used data from several subjects who were declarated positive in a doping control and ten subjects who were injected with nandrolone. We took a sample of urine from all of them. These samples were analysed by gas-mass Cromatography with the Galán & cols’s technique.

With the results obtained in our investigation, we think that the relation testosterone/beta-estradiol can be an interesting scoreboard for the differentiation endogenous or exogenous of nandrolone’s metabolites.


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P09 Recent results of Anti-doping actions

Christian Hirtreiter¹, Tsuyuki Nishino²

Doping agents are spreading out in all social areas. Besides sports and job affairs, even in partner relations stimulating and activating substances are more and more in use. What EPO is for the cyclists, is a variety of different compounds in other areas of social life. Abusing physical relevant substances gets more and more common.

The poster describes the current situation and latest inventions in this field. In the last decade it is more and more common to use so called brain-doping-substances e.g. Ritalin, Ampakines, Donezepil and Modafinil. The adult-generation used dextrose and caffeine as brain food, nowadays even the children use Ritalin and Donezepil in order to stay more attentive in the lessons and to absorb more. Healthy persons avoided in former days to take pills vice versa the new generation is used to take vitamins and other tablets for various purposes. Although it is claimed from the pharmaceutical industries that there is no addictive potential it is sure not only a miracle to enlarge the cognitive abilities.

The effector-mechanisms and moieties of the mostly used substances are described and it is also shown the result of a survey is shown. Recent results of different clinical studies are evaluated. Many of the substances were created in order to heal diseases and the long-term effects are not taken into account in every case. Therefore we compare the chemical structures and draw conclusions why the substances might cause unforeseen side effects especially during the adolescence. The results of questionnaires are stated, where scientist which took caffeine in order to prolong there learning time during their own study period report about their experiences 10 years ago and the effects on their behaviour with caffeine nowadays.

1. http://www.polizei.bayern.de/lka/ and personal communications

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Anabolic androgenic steroids (AAS) supplementation leads to decreased serum testosterone (TS) concentration and impaired spermatogenesis [1, 2]. Leydig cells (LC) are the only cellular components that have the capacity to produce TS from cholesterol. To date, little is known about the effect of AAS on the activity of the key steroidogenic enzymes in the LC of trained and untrained individuals. It is also obscure whether AAS treatment can provoke changes in the apoptotic proteins Bcl-2 and Bax levels in testicular germinative and/or somatic elements. In this relation, the purpose of the present work was to study the effect of AAS on the serum TS level in parallel with the activity of LC 3β hydroxysteroid dehydrogenase (3βHSD), the NADH2 cytochrome-C-reductase, as well as apoptotic markers Bcl-2 and Bax expression in testes of endurance trained rats.

Twenty male Wistar rats were trained on treadmill with submaximal loading for 8 weeks. Half of them received nandrolone decanoate (TND) and the other half - placebo (TP) for the last 6 weeks of the experiment. Ten rats were sedentary and served as controls (C). At the end of the experiment serum TS levels were measured and on testicular sections enzymohistochemical and immunohistochemical reactions were performed.

Our results showed a decrease of 3βHSD (P<0.01; P<0.01) and NADH2 cytochrome-C-reductase activities (P<0.001; P<0.001) in rat LC after treatment with AAS compared to both C and TP groups. These results correspond with the established lower TS serum levels in TND rats than those in C and TP rats (P<0.001; P<0.05). In TP animals compared to the controls there were lower 3βHSD activity in parallel with decreased TS level and higher NADH2 cytochrome-C-reductase staining (P<0.001; P<0.01; P<0.01). In comparison with C and TP rats an increased Bax (P<0.05; P<0.05) and a decreased Bcl-2 (P<0.001; P<0.001) expression in LC of TND group were observed. In contrast, in TP group Bcl-2 intensity was stronger than the controls (P<0.01). The differences in Bcl-2 and Bax expression resulted in a lower Bcl-2/Bax ratio in the TND groups compared to C and TP group (P<0.001; P<0.001).

In conclusion, AAS suppress the activity of key steroidogenic enzyme in LC of trained rats which corresponds to the established serum TS decrease. The obtained results for the first time demonstrate that AAS treatment of endurance trained rats decrease Bcl-2/Bax ratio in the LC suggesting apoptotic tendency in these cells.

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P11 Health Complaints and Health related Consumer Behaviour in International Theatres: A current Assessment

Pia - M. Wippert, Horst Michna

Due to the long training sessions and in part non-physiological postures, top performance in dance and music places high demands on the human body. This abstract reports a current assessment, regarding the consumption of medication and stimulants in international theatres.

72 artists (45 dancers/27 musicians) from German and Swiss theatres took part in the cross sectional study. The sum of bodily complaints was measured with a derived version of Zerssens’s Complaint List. Responses to the extent of consumption of assistive medication were assessed by direct questioning. The statistical analysis was carried out with descriptive methods, as well as tests for differences.

Active dancers differed significantly to active musicians in the amount of complaints ($t(2,7)=-2.45$, $p<.05$). Especially, they expressed more frequent pains of the musculoskeletal system, gastro-intestinal problems, infections, depression and sleeping disorders. They consumed more medication, stimulants, alcohol and tobacco, whereby however, only tobacco consumption revealed a significant effect ($\text{Chi}^2(1)=4.37$, $p<.05$). With dancers, the average number of cigarettes per day was around 19 cigarettes and for musicians around 13. Medication was used by only 21% of the dancers, of which 50% consumed strong pain killers and 38% consumed weak to medium strong pain killers. The remaining 12% consumed anti-inflammatories. In the group of musicians, 11% express sole use of homeopathic medication and medicine against colds. In both groups only caffeine is mentioned as a stimulant.

The groups under study come from elite, professional theatrical institutions with consequent high levels of performance, making the consumption values stated seem far too low- especially in comparison with findings from elite, professional sports. This refers to both the dancers and musicians. Especially amongst the musicians many suffer from symptoms related to their profession, such as tinnitus and problems of the fingers and sinews, which pose an immense threat to their career. Amongst the dancers, the high exertion afforded by the entire musculoskeletal system requires extended periods of rest. The need to cope with constantly recurring stage-fear is an additional factor. Here, the hidden numbers of those who deal with these problems using stimulants or tranquilisers is high. Due to this, and in light of social desirability effects, the results must be interpreted carefully.


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P12 Effect of Spirulina food supplement on blood morphological parameters, biochemical composition and on the immune function of sportsmen

Kazys Milasius*, Ruta Dadeliene

Of highest biological value are natural concentrates of optimally combined substances produced by nature. One of food supplements of this kind is dietary Spirulina produced by the Tianshi firm (China). It is a most rationally balanced food supplement of a high biological value; it satisfies the needs of the whole body, including its immune system. The aim of the current work was to assess the effect of the multicomponent natural food supplement Spirulina on the physical development, blood morphological, biochemical picture and immune function of sportsmen.

The study cohort comprised 12 sportsmen (age 20-22 years). They were using tablets of Spirulina, a dietary product of the company Tianshi for 14 days. Physical development was determined with the aid of standard methods. The general blood picture was analyzed with the aid of a Micros-60 hematological analyzer (company ABX DIAGNOSTICS, France). Lymphocytes and their subsets were analysed by flow cytometry (FACSCalibur, Becton Dickinson Immunocytometry Systems (BDIS, USA)) and the absolute and percentage values were calculated. To evaluate immune function lymphocyte blasttransformation response to mitogens was studied.

Investigations carried out on endurance-training sportsmen showed that a 14-d administration of Spirulina exerted a positive effect on blood morphological composition indices and its biochemical changes. The results of our study confirm the positive effect of Spirulina food supplement on the quantitative parameters of immune system. Part of the study cohort after weeks showed a tendency of normalizing CD3+, CD3+, CD4+ lymphocyte count: positive changes were still present two weeks following the interruption of Spirulina intake.

Immediately following the 14-d period of Spirulina administration, parameter shifts in the sportsmen’s blood composition showed positive changes. Under higher than medium physical loads, the number of lymphocyte subtypes characteristic of specific immune response, particularly CD3+ (T lymphocytes), CD3+CD4+ (T helpers/inductors) has a tendency to decrease with increasing the number of CD3- CD16+ CD56+ (natural killer cells). Lymphocyte response is enhanced by mitogen stimulation. The Spirulina food supplement, based on microalgae, exerts a positive effect on the quantitative indices of immune response: the number of T helpers/inductors.


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General practitioners (GPs) could be important participants in the doping prevention, but it is reported that their knowledge and experience are insufficient to play this role [1, 2]. General medicine is a newly created speciality in Bulgarian Healthcare system and the GPs’ Union is founded by physicians with heterogeneous medical majors and professional experience. The level of Bulgarian GPs’ knowledge of and their attitude to doping in sport as well as how often they have been confronted with doping problems in their everyday practice is not known. The aim of the present study was to investigate the GPs’ attitude, self-estimation of their knowledge and the frequency of their consultations concerning doping. The sample of the study included 112 randomly selected GPs (39.3% men), whose practices are situated in Plovdiv region, the second largest in Bulgaria. The mean (SD) age of the participants was 42.7 (8.8) years and the mean duration (SD) of their professional medical practice and GP practice were respectively 16.5 (8.6) and 4.8 (1.5) years. The participants completed a self-reported questionnaire. From all the GPs 5.4% admitted to have consulted regarding doping in the last 12 months before the study and this percentage is lower than those reported in other countries (1). However 9.8% reported that they have been asked to prescribe doping agents. The most common substances determined by respondents as prohibited in sport were amphetamines (100%), anabolic androgenic steroids (99.1%), diuretics (90.2%). The majority of GPs rated their knowledge about doping as insufficient and almost all (95.5%) indicated a need to improve it preferably by using an Internet site in Bulgarian (83.2 %), courses, lectures (81.3%) and manuals (42%). The majority of GPs (90.2%) considered doping usage as unacceptable at all and none of them would prescribe a doping agent without a medical indication. Doping use was considered by most of the respondents (64.2%) as a problem of all people practicing sport and a need of preventive anti-doping programs in sport schools were determined by 67.9% and in all high schools by 59.8% of GPs. In conclusion, most GPs considered that their knowledge about doping is insufficient and would like to improve it. Our results show the need of doping educational programs having been harmonized with the specific work of this target group in Bulgaria


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P14 Coaches and athletes and their role in doping prevention - empirical data

Christiane Peters*, Peter J. Selg, Jezabel Ohanian, Katharina Habermann, Thorsten Schulz, Helmut Pabst, Horst Michna

The major aims of doping prevention are the athletes and the coaches. With regard to doping there is just little data known about the coaches’ knowledge and their point of view [1]. Therefore, we decided to set out a project (VF 0407/03/41/2003-2004, supported by the BISP/Bonn/Germany) to examine doping related state of knowledge of athletes and coaches from diverse sports associations as well as flow of information.

By means of a written survey, we asked 620 coaches of different levels (rate of return 41%) and 1757 high-level athletes (handicapped and non-handicapped; rate of return 46%) about several doping related aspects. One out of two coaches is regularly confronted with doping issues by their athletes. Main topics are hereby biomedical side effects (15%), nutritional supplements (16%), doping controls (12%) and fairplay (12%). Despite this extensive confrontation with the topic the majority of the coaches (62%) quote to be rather bad or well informed about doping. Just 50% of them owned the current forbidden list and just 58% knew the World-Anti-Doping-Code. However, most coaches are not proactive but want to be informed by their sports association. For over 90% of the coaches it is important to stop doping and to reach this goal they propose a better information of the athletes (17%), a delivery of the current information flyer to all squad members (14%) and the integration of the doping issue into the educational trainings curricula of coaches.

Additionally, a lot of athletes claim to frequently think about doping related topics whereas the coach is their main contact person. About a half of the athletes (52%) have heard about doping issues at their squad meetings. The information was given by the coaches in the most cases (45%) and in 19% of the cases by the physician. Three quarter of the athletes are not proactive at all but were informed by colleagues or other parties. Often national anti-doping associations, diverse flyers or internet information are unknown by athletes. We conclude, that there are urgent needs to change the information policy of sports associations, Olympic training centres, coaches and physicians. Coaches need to use the current knowledge on doping to convince their athletes (of all levels) of a doping-free sport.


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P15 Sports physicians and their role in doping prevention - empirical data

Peter J. Selg*1, Christiane Peters1, Thorsten Schulz1, Helmut Pabst2, Horst Michna1

Recent publications quoted the performance enhancing drug abuse as an increasing problem of "public health" [1-3]. The physician plays hereby an important role, as he is an important contact person, who could recognize biomedical side effects and take a very important part of doping prevention. To characterize the opportunities of advancement of the sports physicians trainings on doping issues we decided to set out an empirical study of the knowledge and attitudes towards doping of the sports physicians (VF 0407/03/41/2003-2004, supported by the BISP/Bonn/Germany).

A total number of 2667 physicians (all qualified in sports medicine) were included into the survey and were divided into two subgroups: While the first group included all physicians in the state of Bavaria (n=2404) running their own surgery the second one sums up all German team physicians being members of a sports association (n=263). An anonymous questionnaire about doping related knowledge, flow of information, observed abuse by athletes as well as preventive strategies was forwarded.

Rate of return of the questionnaire was 18% (n=472) in total, 16% (n=392) among the Bavarian physicians and of 30% (n=80) among the German team physicians. A general demand on doping by athletes was affirmed by 62% of all physicians (57% physicians vs. 81% team physicians). More than one third of the sports physicians evaluate (five aries range of marks) their educational trainings (university, specialists, sports physician) in concern of the extent of their teachings on doping related knowledge as insufficient. The content of the prohibited list is quite well resp. well known for just 25% of the sports physicians running their own surgery. Among the German team physicians more than 75% of counts are seen. At the same time all sports physicians see a quite high resp. a high need for extended doping prevention in following sectors: coaches (86%), competitive sports (85%), students (49%) and even medical sector (66%). The sports physicians show an extensive disaffection towards their educational train-ings concerning doping related knowledge. This fact is accompanied by a heteroge-neous and limited knowledge of the sports physicians, especially the physicians running their own surgery seems to be less qualified. Therefore, doping prevention should be integrated much more into the corresponding medical curricula.

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**P16 Analysis of the mechanism of action of different anabolic agents in bovine tissues to develop an expression pattern for drug screening**

*Martina Reiter, Vanessa M. Walf, Arne Christians, Michael W. Pfaffl, Heinrich H.D. Meyer*

In this study the effects of the anabolic agents melengestrol acetate (MGA), trenbolone acetate and zeranol were analysed in different bovine tissues (liver, muscle, uterus). Using quantitative RT-PCR, the gene expression of specific genes, influenced by the anabolic agents, should be identified.

The selection of candidate genes varied between the different tissues because of the different hormone induced pathways in every single organ. To identify influenced pathways, all candidate genes were selected and separated in functional groups: angiogenesis, apoptosis, cell cycle, endocrine factors, energy metabolism, inflammatory factors, muscle function, oncogenes, protein metabolism and transcription factors.

With the investigation of the regulation and possible function of anabolic sex steroids via gene expression, a preparatory work for the development of an expression pattern for drug screening, was made. Not only in veterinary drug screening but also in the human doping analysis, this can be a promising method to prove the abuse of illegal anabolic agents.


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P17 Erythrocyte aminotransferase as an indirect marker for stimulated erythropoiesis in athletes

Yohan Robinson*, Edgar Cristancho, Dieter Böning

Even though doping with erythropoietin (EPO) is an effective but illegal performance enhancer, a simple and reliable screening-test is still unavailable. Most of the existing direct and indirect detection methods are either too expensive or not sensitive enough. Thus a new approach by estimating mean red blood cell (RBC) age by means of erythrocyte aspartate aminotransferase activity (eAST) – an effective indicator of mean RBC age - was developed.1,2 Previous investigations have shown that eAST was capable to determine RBC rejuvenation in chronic hypoxia.3,4 This study was designed to establish reference values and to evaluate the influence of training status on eAST.

201 female and 169 male individuals residing at low altitude were investigated for serum EPO concentration (sEPO), haemoglobin concentration [Hb], and eAST.5 Furthermore 63 female and 42 male individuals residing and training at 2,600 m above sea level were investigated for sEPO and eAST. Participants were subdivided into trained, moderately trained and untrained. Additionally 22 female and 28 male patients with renal failure receiving recombinant human EPO (rhEPO) were investigated for eAST levels.

For low altitude residents there was no difference in eAST among trained, moderately trained and untrained subjects for either sex (Tab. 1); the distribution of values was approximately normal (Fig. 1). Trained high-altitude residents had higher eAST than untrained high-altitude residents (ANOVA, p<0.05) and male lowlanders (ANOVA, p<0.05). sEPO did not differ between high and low altitude. Patients receiving rhEPO had higher eAST with increasing weekly rhEPO-dose (r=0.25, p<0.05).

Since long-lasting training has no effect on eAST but rhEPO-therapy and high-altitude residency have, eAST-elevation in lowlanders should indicate EPO-doping. eAST-values above the 95% confidence interval (>3.3 U·gHb-1 for males, >4.1 U·gHb-1 for females) are suspicious of EPO-doping.

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P18 Doping prevention strategies in Spain and the importance of social alarm as preventive strategy

Maria Dolores Hinchado*, Esther Giraldo, Eduardo Ortega

The main subject of any sanitary system is prevention. Unfortunately in the fight against doping all investments are focused in development of new techniques for drugs identification and controls and there is not a lot of interest in prevention. Antidoping controls must be considered as a way to guarantee a competition free of drugs and prohibited methods. But the best way to beat doping is through education, information and with the correct medical assistance. Usually most of the efforts try to discover the culprits, but often we forget other actions. We encourage sportspeople to win at any price, the prestige of the team, school, locality, nation which represents are at stake. Therefore huge amounts of money are offered in order to win or to get better results. On the other hand we forget the day-a-day sportsperson’s medical specialized assistance. This problem gets bigger in amateur or recreational level, where most of the users are not checked medically and more often they resort to exogenous stimulants.

The present study considers the prevention actions related to doping control developed in Spain and also the new actions that we propose. Until few years ago, in our country the law about doping was based on the sports field; unlike France, Italy or Belgium which their actions against doping consider doping such as a criminal act. However, it is just passed in Spain the new Law to protect health and to fight against doping in Sports. In this law doping is considered for the first time as a health problem and people who promote or practise doping attempt on public health. The new law promotes different measures in order to prevent and improve sportspeople’s health. So, the fight against doping in Spain is based on the need to inform, educate and to make aware sportspeople about the harmful effects of doping, and moreover to show that the sportspeople can improve their scores without doping.

Finally, in this presentation we also propose to stand out the need to generate social alarm in relation to the side effects of doping on health and a prevention strategy, above all for those who start practising sports.

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P19 Glucocorticosteroids in doping analysis

Radoslaw Jazwiec*, Andrzej Pokrywka, Dorota Kwiatkowska, Ryszard Grucza

Glucocorticosteroids (GCS) were considered, as doping agents by IOC Medical Commission in 1975. But until September 2003, decision on banning them was in authority of particular sport federation. In this year, WADA has set prohibition of this group, as a mandatory rule for all in-competition samples. According to 2006 edition of the WADA Prohibited List - all GCS administered locally are permitted. For drugs administered by inhalations there is a special simplified procedure for obtaining TUE (Therapeutic Use Exemptions) [1].

GCS as pharmacological group are defined by their pharmacodynamic similarity with natural hormones: cortisol and cortison. As other steroid hormones - they migrate into target cells, and act directly on the transcription of DNA. Their main metabolic action is opposite to effect of insulin administration. In contemporary medicine they are used as anti-inflammatory agents, and to prevent the rejection of the transplant by the patient's immune system [2].

GCS effectiveness as doping agents is disputable. The doping effect is not adequate to side effects connected with administration of high doses of GCS. It is also possible, that most GCS positive samples were caused not by intentional doping, but by improper medical use.

Because use of glucocorticosteroids is allowed in some cases, prohibited threshold of 30ng/ml has been set by WADA [3]. The same value for all GCS, caused considerable controversies, because drugs of this group have very various strength of action. There is a scientific project going on (founded by WADA), aimed to set appropriate thresholds for substances of this group.

According to statistics presented by WADA for the years 2004 and 2005, the first year of prohibition of glucocorticosteroids showed that GCS became the second ranking doping agents, after anabolic steroids. In 2005 they were located on the fifth place. During that year the polish laboratory found only three positive samples containing glucocorticosteroids (over 30ng/ml). It is possible that lowering of GCS prohibited threshold would increase the number of these positive samples.


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P20 Resting blood hormones levels and weightlifting performance

Zbigniew Obminski*1, Dorota Kwiatkowska2, Andrzej Pokrywka2, Ryszard Grucza1,2

The goal of the present study was to examine weightlifting performance in relation to resting blood endogenous hormones. Six male athletes preparing to the European Championships (EC) and after that to the Olympic Games were subjected to the study covering long-lasting training period. Levels of cortisol (C) and testosterone (T) were measured in the blood sampled on the each day of six simulated competition and additionally on the other 12 terms. The levels of performance were rated by outcomes of snatch (S), clean and jerk (C&J), and total weight (TW) each of them expressed as percentage of those reached later on the Olympic Game. Differences between changes of the of blood parameters: C, T and T/C ratio, and of athletic performance were tested by analysis of variance with repeated measures followed by the post-hoc test. The results indicated two peaks performance reached during training period. The first one was prior to EC and manifested itself as the best average, relative S (97.9±1.5%), C&J (102.4±2.3%) and TW (100.1±1.4%) despite the lowest hormonal parameters such as mean level of T (15.5±3.5 nmol/L) and index T/C (2.8±2.1). The second one was reached three month after the first one, on the latest simulated competition when the mean examined values were as follows: snatch - 95.5±1.4%, C&J - 102.5±1.5%, TW - 99.2±0.6%, T - 31.3±11.7 nmol/L, and T/C ratio - 7.5±3.3. The best outcome on the Olympic Games i.e. silver medal won the athlete exhibiting moderate T but the lowest intra-subject variability of T during the whole preparatory training. Among 82 observations we noted 14 cases of episodic androgenic hyperactivity expressed as very high T levels each of them exceeding the upper level (41.6 nmol/L) and giving the mean value amounting 51.8±9.7 nmol/L. Majority of these cases occurred after EC. These findings may suggest that lower blood T allows to maintain excellent athletic performance over only short-lasting period. Since the noted cases of hyperandrogenism are hard to explain based on physiology, and generally doping with androgenic-anabolic steroids among weightlifters are more frequent then among the other athletes [1] we may suspect, that prolonged psycho-physical overloading forced some of weightlifters of lower training tolerance to take anabolic steroids. However, that assumption might be judged only by more advanced analysis.


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P21 Searching the reasons for temporary abnormal hormonal status in the healthy athletes. A case study.

Zbigniew Obminski¹, Dorota Kwiatkowska², Andrzej Pokrywka², Ryszard Grucza¹,²

This communication presents cases of abnormal blood cortisolism and androgenism in two endurance trained and six judokas. One male and one female, the modern pentathlon athletes, have been regularly examined throughout a 4-years period and completed 13 exercise studies. The each study consisted of cortisol measures in four blood samples taken in the morning, prior the exertion, and at 3 and 30 minutes of post-exercise recovery. The mean blood cortisol levels in these samples calculated from 12 studies were as follows; in the male: 633±109, 530±131, 616±136 and 793±186, and in the female: 506±177, 367±127, 374±138 and 499±150 nmol/L. However, during the one exercise study, the male and the female athlete exhibited abnormal hormonal status. In the blood taken from the male cortisol levels were: 1518, 1380, 1408 and 1435 nmol/L, and these results were associated with non-physiological testosterone levels reaching almost two-fold the upper limit (41.6 nmol). In the female hormonal abnormality manifested itself as very low levels of blood cortisol: 25, 26, 25, and 19 nmol/L, and very low testosterone levels, on average 0.3 nmol/L, while during the other studies it ranged from 1.3 to 2.8. In the six judokas, 3 males and 3 females, morning blood cortisol and testosterone levels were monitored during training camps. Cortisol levels ranged from 389 to 689 nmol/L, until they had to stop their training activity, and had to be treated with steroidal anti-inflammatory agents. 24h followed by single into knee or elbow joints injections of artificial steroids, endogenous cortisol strongly decreased to the range 21-48 nmol/L. In response to treatment by steroids, blood testosterone levels decreased, somewhat in the males, by 30%, and makededly, 5-6 fold in the females. Some difficulties appear with understanding of hormonal behavior in the pentathlon athletes. They did not report to use any medication. Moreover, despite huge deficits of the endogenous hormones observed in the female, similar to those in female judokas, her athletic performances was quite good. That mentioned adrenal suppression was caused due to negative feedback [1]. In the male athletes blood hypercortisolism and hyperandrogenism were not ever report by others. In summary, for explanation such as blood hormonal abnormality further investigations are required.


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9 SYMPOSIUM PROGRAM

GREETINGS

09:00 – 09:20 a.m.  Welcome & Opening
Rudolf Schilling
Vice-President of TU Munich
Paul Marriott-Lloyd
Programme Specialist Anti-Doping, UNESCO

09:20 – 09:30 a.m.  The Project – Idea and Goal!
Horst Michna
Dean Faculty of Sports Science, GER

SESSION: DOPING IN GENERAL

Chairs: Asterios Deligiannis and Paul Marriott-Lloyd

09:30 – 10:05 a.m.  The Doping Issue
Barrie Houlihan
School of Sport & Exercise Sciences, Loughborough University, UK

10:05 – 10:40 a.m.  Drug Abuse and Doping Behaviour
Patrick Laure
DRDJS– Sports and Public Health, Saint-Max Cedex, F

SESSION: HEALTH SIDE EFFECTS – PART I

Chairs: Katerina Georgieva and Martin Halle

11:10 – 11:45 a.m.  Nutritional Supplements
Christiane Ayotte
Doping Control Laboratory, INRS-Institute Armand Frappier, CND

11:45 – 12:20 a.m.  Anabolic Steroids
Linn Goldberg
Human Performance Laboratory, Oregon Health & Science University, USA
SESSION: HEALTH SIDE EFFECTS – PART II

Chairs: Eduardo Ortega Rincón and Hans-H. Dickhuth

01:50 – 02:25 p.m. Narcotics
Ryszard Grucza
Department of Antidoping Research, Institute of Sport, PL

02:25 – 03:00 p.m. Cannabinoids
Peter Van Eenoo
Doping Control Laboratory, Ghent University, B

03:00 – 03:30 p.m. Gene Doping
Odile Cohen-Haguenauer
LBPA, ENS-Cachan, F
Bernd Gänsbacher
Institute of Experimental Oncology, GER

SESSION: DOPING PREVENTION STRATEGIES

Chairs: Roland Augustin and Carl Müller-Platz

04:00 – 04:30 p.m. ATLAS & ATHENA
Melissa Durham
Center for Health Promotion Research, Oregon Health & Science University, USA

04:30 – 05:00 p.m. Prevention Strategies in Sweden
Bengt O. Eriksson
Swedish Doping Commission Goeteborg, SWE

05:00 – 05:15 p.m. Conclusion & Closing
Horst Michna

ROUND TABLE: PERSPECTIVES OF PREVENTION

Chair and Moderator: Linn Goldberg

05:15 – 06:15 p.m. Barrie Houlihan (UK) Luis Horta (P)
Linn Goldberg (USA) Patrick Laure (F)
Hans-H. Dickhuth (GER) Thomas Kistler (GER)
Dedication

In memory of Horst Michna
a much valued colleague and good friend
and initiator of this project.

Thanks for your large commitment in the
fight against doping in sport and the possibility
that we could go a piece of the way together.