Biomedical Side Effects of Doping

Project of the European Union
Preface

As many of you will know, I have a keen interest in sport in general and in the fight against doping in particular. In 1999 the Commission adopted a Community support plan to combat doping in sport and has since, in close co-operation with the Member States, waged a tireless campaign in this field.

Among its actions, the Commission has set aside, in 2000 and 2001, a total of some 5 million euros to help finance projects designed to help in the fight against doping.

The project of the Deutsche Sporthochschule to harmonise knowledge about the biomedical side effects of doping is one such worthwhile projects financed by the Commission.

The media publicises doping scandals but there is in general a lack of knowledge of the side effects of doping, not only among the general public but among athletes and the sporting world also. Greater knowledge of the immediate and of the long-term physical and psychological effects of doping is essential. Trainers and athletes, particularly young athletes, should have access to this information for only then may they know the full implications of a decision to take illegal substances.

The work of the Deutsche Sporthochschule will aid considerably in this and I congratulate the Deutsche Sporthochschule for their valuable contribution to the fight against doping and on the production of this manual.

Viviane REDING
Foreword

Since the Olympic Games in Munich in 1972, the fight against doping has become a task of the Federal Institute of Sport Science (BISp). Following the Olympics in 1972, the Federal Institute of Sport Science took over the promotion of doping analysis which was conducted by the then young lecturer Dr. Manfred Donike at the Institute of Biochemistry at the University of Cologne. This collaboration with the later head of the Institute of Biochemistry at the German Sport University Cologne lasted until his sudden death in August of 1995.

Under the unification of East and West Germany contract it was decided that the IOC accredited laboratory of the former GDR in Kreischa (near Dresden) was to stay in operation. This laboratory was progressively equipped with new staff and materials.

As a legal basis a club structure suitable for sport was created, in which the National Sport Association, the German Sport Association and the National Olympic Committee as well as the federal states, districts and the municipalities take part, in differing capacities. The financing of the present Institutes for Doping Analysis and Sport Biochemistry (IDAS) is provided by the federal budget through the BISp.

Technical committees and specialist advisory bodies were set up during 1993 to support the BISp as consultants. Since then, the BISp has taken on more and more tasks in the fight against drug misuse.

In sponsoring research, the BISp is not only occupied with the further development of analytical procedures in the laboratories, but also with the development of new methods to test for dope such as using growth hormones produced through a recombination process. In addition to urine, other types of test specimens are under consideration such as blood (red-white series Vol. 86 "Blood and/or urine for doping controls") and hair (Red series Vol. 2000/1 "Progress in Hair Analysis for Illegal Drugs").

In close co-operation with the task group "Anti-doping" of the on-going conference of the Minister of Sport/national senators, we organised an international symposium with the Netherlands, Austria and Switzerland in Autumn 1997, which primarily considered the question of preventing drug misuse. A further research assignment is the historical reassessment of the organised doping in the DDR and its consequences. There have already been reports of damage to health resulting from the use of anabolic substances.

We are promoting further projects dealing with health damage resulting from doping. In this context we have initiated investigations on side effects of anabolic substances at the molecular level and their effects on the heart musculature. Several respected publications warn about the threat of health damage due to the side effects of anabolic substances and other doping substances (e.g. The Athletes Brochures "sudden death through cardiac arrest", Red series Vol. 99/12 "Performance manipulation – a danger for our athletes", "Doping controls"). Such publications serve the transfer of scientific knowledge into practise.

The subject of health damage was discussed by German scientists at several symposia. Prof. Michna was a permanent guest at these symposia. In particular, the longstanding collaboration with the German Sport University and the Institute of Morphology and Tumour Research provided a good basis for a successful collaboration on international research projects, which could not be realised on a national basis by the BISp.

On the international level much research on the effects and side effects of drug misuse have been carried out. To achieve a suitable evaluation of the state of the art, national borders must be crossed and it must be strived to correlate their knowledge with ours. A fusing of the total existing state of knowledge over the health consequences of drug misuse is always the starting point of new still necessary research strategies. It is also the task of the BISp to promote research in the area of combating drug misuse.

The BISp has the assignment of promoting the transfer of research results into practice.

The national objectives of the Federal Institute of Sport Science are therefore conform with this project.

Dr. Martin-Peter BÜCH
Director / BISp
Preamble

Dear reader! Dear athlete!

This manual is the summary of an international symposium organised at the German Sport University in Cologne in 2001. The European Union offered the financial support to the undersigning research centres from the six different European countries to summarise the knowledge on biomedical side effects of doping for the public. We, the collaborators of this EU project and speakers at this symposium are professionally engaged in both research and teaching of scientific aspects of doping. In addition to the European colleagues two distinguished experts from the United States were kind enough to join us.

The goals of this symposium were as follows:

- Collection of information about possible both actual and long-term health side effects of doping in competitive sports with regard to biomedical and psychological side effects of doping in athletes.
- Harmonising the knowledge concerning biomedical side effects of doping.
- Realisation of an international symposium about biomedical side effects of doping to disseminate knowledge.
- Compile a manuscript including all presentations as an aid for the initialisation of lecture series concerning these topic at the universities.
- Appropriation of these information to all European countries.

This symposium in Cologne was, to the best of our knowledge, the first of its kind: it was attended by almost 200 participants from 25 different countries. The resonance given to us organising such a symposium expressed in the newspapers was impressive.

Especial credits should certainly be given to the colleagues from Prof. Michna: Dr. Christiane Peters and her team colleague Dr. Thorsten Schulz and last but not least Ms. Suse Wolff, who was most helpful in solving our pressing problems during the time of the symposium preparation.

The goal of us was not to provide the latest scientific knowledge for the experts: our intention was to provide an overview for those interested in the topic. Nevertheless, we appreciate your further questions and remarks: therefore, our (e-mail) addresses are included. We look forward to your comments.

Finally, we would like to emphasize our wish that this should not have been the last time such a symposium was organized. Based on inquiries in our countries we feel that such a symposium should be organised on an annual basis.

Dr. Carl MÜLLER-PLATZ (Federal Institute of Sport Science/ Germany)
Prof. Dr. Asterios DELIGIANNIS (Aristotle University of Thessaloniki/ Greece)
Prof. Dr. Eduardo ORTEGA RINCON (University Extremadura/ Spain)
Prof. Dr. Harm KUIPERS (University of Maastricht/ Netherlands)
Prof. Dr. Jorge PASQUALINI (Steroid Hormone Research Unit/ France)
Dr. Timo SEPPÄLÄ (National Public Health Institute/ Finland)
Prof. Dr. Dr. Horst MICHNA (German Sport University Cologne/ Germany)
Personal remarks of the organiser

“There are two kinds of people, those who got the credit, and those who did the work” (Indira Ghandi).

The work was done by my colleagues: Dr. Christiane Peters, Dr. Thorsten Schulz and Ms. Suse Wolf.

I had the privilege to meet the fine colleague from the Federal Institute of Sport Science Dr. Carl Müller-Platz: together with him, we created the idea of an international symposium on biomedical side effects of doping after the European Union advertised the chance of hosting such a specific program. Within the “unrealistic” timeframe of the six weeks, Dr. Müller-Platz and I encouraged our scientific friends to join us in applying for a grant and to contribute to the symposium by holding a lecture. Although these very distinguished colleagues are head of research institutes in the fields of sports medicine and possess high responsibility both in research and teaching at their universities we got only one single answer from all of them: “We will make it happen; it is worth the goal!” And finally, the European Union made it possible. To be honest I believe that the colleagues from the European Union were somewhat surprised that seven experts were instantaneously willing to cooperate. I appreciate the efforts made by those colleagues to submit a manuscript and to hold a lecture in Cologne. Those who did the work – Dr. Peters, Dr. Schulz and Ms. Wolff – did not get any financial support by the European Union. Those colleagues and the speakers should be given the credit.

Host MICHNA
Abstract

With regard to the scientific knowledge of the side effects of doping in competitive sports, there is a tremendous lack of information in Europe in the public. This issue is very well reflected in media where reports on side effects of doping in competitive sports just report on death after doping but do not touch the severe side effects of doping for instance with anabolic steroid hormones.

It was therefore the goal of this manual to collect information and provide novel views on possible health side effects of doping in competitive as well as in recreational sports with regard to medical and psychological effects on athletes both during the years of competition and as long-term side effects.

Depending on the type of prohibited substance as well as the amount and duration of intake the occurrence of health side effects can not be disclaimed. A lot of articles can be found ranging from case reports up to scientific studies. Numbers of people involved in these studies vary as well as used methods (interviews, questionnaires, biomedical parameters, etc.) do. Because results of literature are inconsistent and sometimes unclear within this manual, scientific knowledge of biomedical side effects of doping of all classes of banned substances mentioned on the IOC doping list were described by well known experts working in this field. Besides the metabolic aspects of drug abuse, side effects both in adulthood and in childhood are analysed. Furthermore, historical aspects of doping are described in general and especially with regard to the national ordered doping practices of the former GDR. Moreover, special attention was given to the severe side effects of children. In addition, the actual issues of an uptake of compounds from the environment with hormonal potential possible risks of nutritional supplements use are described.

A major aim of the manual was to harmonise the knowledge of biomedical side effects at an European level and to make the scientific based knowledge available and understandable to the public.
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1 Introduction

Christiane Peters and Carl Müller-Platz

1.1 History

Already prior to 1894 when Pierre de Coubertin and the new founded International Olympic Committee (IOC) heralded the “modern” Olympic Games different substances were used to enhance physical performance in sports.

Early information concerning drug abuse are dated before Christ. Finlay and Pleckert (1976) described that in the ancient Olympic Games dated 668 before Christ the winner of the 200 m race already used a special diet of dried figs. In the third century before Christ the Greek Galen mentioned that during the Olympic Games athletes tried to enhance their physical performance by the use of stimulants as well. Furthermore, in preparation for the competition wine or brandy were drunk and mushrooms were eaten believing that performance could be enhanced by these special methods (Voy 1988, Verroken 2001).

Gladiators during the old Roman Empire used strychnine as well as knights bachelor during the Middle Ages in order to improve their performance after injuries and thus increase their chances of survival (Donohoe and Johnson 1986, Voy 1991).

In the 19th century use of several ergogenic substances such as alcohol, strychnine, caffeine, opium, cocaine etc. are mentioned in literature (Tipton 1997). During the marathon race of the 1900 Olympic Games, brandy and strychnine were administered from a physician to his athlete before winning the race (Giller 1980).

Based on positive experiences of the application of stimulants to soldiers during the Second World War to enhance their attention and reduce fatigue, stimulants were widely used in sports during the 40’s and 50’s (Verroken 2000). First use of amphetamines was reported by an eye-witness already during the Berlin Olympic Games in 1936 by Mondenard, who collected all information about the Olympic Games including a lot of eye-witness reports concerning misuse of doping substances (Mondenard 1996).

In the early 50’s (Helsinki 1952) discussions concerning the abuse of anabolic steroids in Soviet weight-lifters commenced (Todd 1987). Following these individual cases drug abuse in sports widely increased during the 60’s.

The overdose of amphetamines followed by the death of the Danish cyclist Knut Enmark Jensen during the 1960 Olympic Games in Rome, resulted in several anti doping activities including the IOC doping definition in 1964 followed by the first anti doping laws in Belgium and France in 1965 (Voy 1988).

In parallel to governmental and sports authority activities, drug testing started (Guezennec 2001). Brundage, president of the IOC during these period, stimulated the formation of the first Anti Doping Commission. In 1966 the construction of national Anti Doping Committees were intended to realize enlightenment campaigns against doping as well as to stimulate the International Federations to remit doping rules and to avoid that drug positive athletes were allowed to take part in Olympic Games.

Whereas in the early 60’s tests were not sensitive enough to clearly identify positive samples, the Medical Commission of the IOC was established in 1967 with the major task of doping control. Furthermore, “doping” was integrated in the Olympic rules for the first time. In the same year the IOC published the first list of prohibited doping classes including stimulants, narcotics, antidepressant drugs and tranquilizers. Furthermore, sanctions were described as well as some substances mentioned as prohibited under certain circumstances. Anabolic steroids have been used by some cheating athletes but have not been penalized. Since 1971 cocaine is banned, too.

Although 668 doping controls were conducted already in the Mexico City Olympic Games in 1968, proper doping controls only started at the Olympic Games 1972 in Munich. From the 2079 samples seven were analysed as positive.

Great progress in clinical science and availability of therapeutically helpful anabolic steroids resulted in a more frequent use of these substances in sports. Efficient talent screening and systematic and national ordered doping was established in the GDR which was followed by international success in nearly all kinds of sports. Because anabolic steroids could not be detected by doping controls during the early phase they were not mentioned on the first doping list as a banned class of compounds until 1974 (Mondenard 1996, Cowan and Kieman 1997).

After establishing these new analytical methods, alternative substances such as testosterone became interesting again. Because of their wide panel of side effects they were denied at the beginning but renewed now. Methods to evade the AAS (anabolic androgenic steroids) positive testing were searched for and established. During the “pre-competition bridging program” of the GDR during the last weeks before competition, athletes switched from xenobiotic steroids to testosterone which was not detectable until 1983 (Franke and Berendonk 1997). But
already in 1984 all samples were tested concerning the testosterone/epitestosterone ratio, a new method to detect testosterone abuse in the doping control panel.

During the 11th Olympic Congress in Baden-Baden in 1981 the head of the Medical Commission Prince Alexandre de Merode, who also was responsible for the anti-doping policy of the IOC reported about success of doping controls but also called for additional education programs against doping. Declarations of athletes and trainers against doping were the origin for the later development of the Olympic Charter. During the first permanent World Conference against Doping in Ottawa in 1988 the Olympic Charter was decided on and presented to the UNESCO and supported by them afterwards. The aim of the Olympic Charter was and still is a world wide harmonising of the fight against doping.

Due to new developments in sports so-called beta-blocker (1985), diuretics (1986) and masking agents like probenecid (1987) were added to the doping list of banned substances as well as blood doping and pharmacological, chemical and physical manipulation of the samples. For the Olympic Games 1988 in Seoul the renewed list already consisted of six classes of banned substances, doping measures and classes of substances which use was restricted.

While blood doping became more frequent in the 80’s to enhance oxygen capacity in endurance sports, alternative use of erythropoietin (EPO) became increasingly prominent. Recombinant EPO is available since 1985 and was originally intended for clinical use of anaemic patients with impaired EPO production. In the meantime genetically engineered human growth hormone (hGH) is available, too. Before 1985 hGH could only be obtained from cadaveric pituitary extracts and the transfer of infectious diseases was risked.

These new trends in drug abuse in sports resulted in an extension of the doping list of the IOC. EPO was classified first as a doping substance by the International Ski Federation in 1988. Shortly afterwards growth hormone and other peptide hormones like ACTH and erythropoietin were listed by the IOC and banned during the Barcelona Olympic Games in 1992.

During the 80’s athletes using anabolic steroids were able to pass the doping control system by using the above mentioned switching methods. Anabolic steroids were generally used during training to develop their effects during these training sessions. Anabolic steroid abuse stopped in time, resulted in the fact that a lot of cheating athletes could pass doping controls during competitions without any problems. Therefore, in 1988 the National Olympic Committee of the former West-Germany decided to implement additional out-of-competition controls. Because several new substances which were quite similar to listed ones were used to enhance physical performance in sports without any consequence, in 1993 the IOC decided to add “related substances” to the listed classes which meant related to the chemical structure and/or pharmacological action.

Although the Council of Europe realized the doping problem much earlier they opened an “Anti-Doping Convention” for signature in 1989 and developed the Clean Sports Guide which is an education and information guide on sport without doping. The European Community requested all member countries to spread a special code of behaviour in sports without doping and to support initiatives of the European Community concerning information and education against doping. In parallel, the World Health Organisation (WHO) included health aspects due to doping in sports within their general fight against drugs in the society. Following this a lot of national anti-doping campaigns were started in several countries.

The Olympic Charter against doping in sports does not only mention that doping in sports is unhealthy but also a violation against ethics in sports (IOC 1990). In parallel, literature not only focuses on ethical aspect of doping but also on research concerning the effectiveness of drug substances to enhance physical performance as well as on health side effects. While effects of stimulants and narcotics were investigated mostly before the 80’s, a lot of scientific results about anabolic steroids were published in the 80’s due to the “Anabolic Phase” in sports. In parallel to new trends in doping with peptide hormones actual studies deal with the effects of EPO and hGH and were published now.

Resulting knowledge mostly contains health effects and health side effects of therapeutical drug abuse. Due to information of cheating athletes usually much higher dosages were used in sports than in therapy. Literature show a lack of knowledge about health side and adverse effects concerning use of such amounts of drugs as well as long-term side effects.

Furthermore, use of several drugs in combination in sports become more frequent and nearly nothing is known about the interaction or counteraction including a higher risk of side effects.

Moreover, cannabinoids (marijuana, hashish) and consumption of other social drugs are increasingly becoming a problem not only in society but also in sports. Therefore, the doping list must constantly be adapted to the changes in the practical use of doping substances in sports.

Because of the wide range of offered nutritional substances used also in recreational sports sometimes, it is difficult to define where allowed nutritional support ends and doping starts. Creatine for example is widely used in high elite sports as well as in recreational sports, body-building and fitness sports and results of some studies report increased performance. Up to now creatine is not mentioned on the doping list and no health risks are described in literature when used only for a short period. But nothing is known about long-term effects of high
amounts of these substances or combinations of several products. Therefore, there is special need for further investigation.

Furthermore, special attention should be given to the purity of all these offered products. Some positive doping cases mentioned that to their knowledge they never have taken doping substances but only nutritional supplements. Results of analysed products could show that nutritional supplements can be contaminated (Geyer et al. 2000), another growing problem in this field.

All these facts may point out that doping is not only a problem of high elite sports but the use of doping substances in leisure sports or even for body shaping is also a problem of society. A lot of drug abuse in sports takes part in recreational sports without any possible control. The health side effects are the same, perhaps higher because of the higher amount of taken drugs.

Being aware of these growing problems the European Union reinforced their activities within the fight against doping within the last years. Projects like the British “GH 2000” were financially supported by the European Union in cooperation with the IOC. Moreover, with active support of the Council of Europe the World Anti Doping Agency (WADA) was created to promote and coordinate the fight against doping at an international level.

Furthermore, the European Union started a great number of anti doping campaigns. During the last two years they called for proposals and financially supported a lot of anti doping projects in Europe. Special attention was given to information campaigns with the aim of protecting young athletes, to sensitise and inform them about health risks, side effects and ethical values and supply them with knowledge in their fight against doping.

In future, the complexity of the fight against doping will increase. High quality research concerning doping analytics is requested as well as epidemiological data concerning the amount of the problem and the motivation of athletes to take performance enhancing drugs not only on a high elite sports level. Furthermore, knowledge about biomedical side effects has to be harmonised and enhanced to support information campaigns and educational programs which must be forced to prevent young athletes concerning the abuse of doping substances. They should be accompanied by further enlightenments concerning national and international distribution of drugs which must be analysed more in detail to support doping prevention.

The aim of the involved scientists was to harmonise the knowledge about biomedical side effects of doping as a general basis for further campaigns. Therefore, this manual is well targeted to be used in lecture series.

1.2 References

1.3  **Addresses**

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2 The Epidemiology of Doping in Sport
Charles E. Yesalis and Michael S. Bahrke

2.1 Role of Epidemiology

Epidemiology can play an important role in analyzing the problem of doping in sport. This includes estimating the incidence and prevalence of doping as well as identifying and profiling the population at greatest risk of using performance enhancing drugs (PEDs).

In addition, epidemiologic methods are central in determining whether or not a drug is in fact a performance enhancer. Moreover, epidemiology is at the heart of the process of identifying the physical and psychological health effects of doping. A key epidemiologic concept that is critical in constructing a causal model of the doping predicament is the “Epidemiologic Triangle”, i.e. the dynamic interaction of the host (the athlete), the agent (drugs), and the social environment (see tab. 1).

Tab. 1: The role of epidemiology.

<table>
<thead>
<tr>
<th>Identify:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>o Population at risk</td>
<td></td>
</tr>
<tr>
<td>o Effects on performance</td>
<td></td>
</tr>
<tr>
<td>o Effects on physical and mental health</td>
<td></td>
</tr>
<tr>
<td>o Dynamic interaction of host – agent – environment</td>
<td></td>
</tr>
</tbody>
</table>

To proceed with an epidemiologic analysis of doping, we first must agree on a definition of doping, just as we would need to agree on a definition of any disease being studied (see tab. 2). Officials of the former GDR argued that for athletes whose rigorous training regimens adversely affected their hormonal profiles, testosterone replacement therapy was not doping, and should be permitted.

Analgesics do not enhance performance as much as they allow athletes who are injured to perform at or near their pre-injury levels. Is using aspirin doping? More and more athletes, including golfer Tiger Woods, are availing themselves of lasik eye surgery to improve their vision. Is that doping? Although they are not found on “banned drug lists”, one could persuasively argue that creatine, sodium bicarbonate, altitude training, and psychological techniques are all performance enhancers. So again, before we proceed further in an epidemiological investigation of doping, we must agree on a definition of “the disease.”

Tab. 2: Define the “disease”.

<table>
<thead>
<tr>
<th>What is doping?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>o Performance enablers vs. enhancers</td>
<td></td>
</tr>
<tr>
<td>o Hormone replacement</td>
<td></td>
</tr>
<tr>
<td>o Analgesics</td>
<td></td>
</tr>
<tr>
<td>o Lasik surgery</td>
<td></td>
</tr>
<tr>
<td>o Creatine</td>
<td></td>
</tr>
<tr>
<td>o Sodium bicarbonate</td>
<td></td>
</tr>
<tr>
<td>o Altitude training</td>
<td></td>
</tr>
<tr>
<td>o Psychological techniques: hypnosis, imaging</td>
<td></td>
</tr>
</tbody>
</table>

Going back to my original charge of applying an epidemiologic perspective to doping, we should start by identifying the population at risk (see tab. 3).

Tab. 3: Challenges to identify the population at risk (PAR).

<table>
<thead>
<tr>
<th>PAR:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>o Accuracy</td>
<td></td>
</tr>
<tr>
<td>o Social desirability</td>
<td></td>
</tr>
<tr>
<td>o Extremely secretive behavior – a violation of:</td>
<td></td>
</tr>
<tr>
<td>o Rules of sport</td>
<td></td>
</tr>
<tr>
<td>o Criminal law</td>
<td></td>
</tr>
<tr>
<td>o Social norms</td>
<td></td>
</tr>
</tbody>
</table>

Doping is a controversial and socially undesirable behaviour and, not surprisingly, it is an extremely secretive behaviour. In my experience, many athletes would be much more willing to admit to either striking their spouse, or using illicit drugs (e.g., cocaine or marijuana) than they would admit to doping. Therefore, when attempting to assess the incidence and prevalence of doping, the accuracy of the data must be fully scrutinized.
We can all recall examples of athletes refusing to acknowledge their use of performance enhancing drugs such as many of the riders who participated in the 1998 Tour de France. When athletes are caught in a doping test, they almost always say “Oh, I wonder how that got it into my body” or “I would never take drugs” and so on. So what are strategies to identify the population at risk of doping (see tab. 4)?

Tab. 4: How to identify the population at risk?

Strategies:
- Drug tests
- Scientific surveys
- Government investigations
- Investigative journalism

2.2 Drug Tests

Clearly, drug tests would be one method that comes to mind. Until the Ben Johnson scandal in the 1988 Seoul Olympics, the public thought drug testing generally worked well to deter doping: that only a very small percent of athletes doped. However, a journalist at that time had the good sense to ask: “How did Ben Johnson pass the previous 19 tests that he had undergone?” The answer to that question was the beginning of drug testing’s “fall from grace”. This fall was hastened by the detailed documentation in the news media of widespread doping over three decades by the highly successful athletes of the former GDR (without a positive drug test!). This, in turn, was followed in the early 90’s by the Communist Chinese drug-assisted dominance in world sports. Unfortunately, several years passed and numerous Olympic medals were won and many world records were shattered before positive drug tests tainted the Chinese victories. Any remaining apologists for drug testing were cowered by the sheer magnitude of the Tour de France fiasco of 1998. A doping scandal uncovered not by the drug testers, but by French Customs police!

The public has increasingly heard from experts that only stupid or careless athletes ever get caught in drug screens. I think if we look at the overall effect of drug testing on the level of doping over the past three decades, we would need to conclude that its failures have dwarfed its successes. However, what significance does all this have for an epidemiologic analysis of doping? While there appears to be only a smattering of false positive drug tests, it has become public knowledge that there is an “epidemic” of false negatives. Therefore, the results of drug test are of little or no value as estimates of the incidence or prevalence of doping.

2.3 Scientific Surveys

Another strategy to estimate the incidence and prevalence of doping is the use of scientific surveys. My experience with those surveys is that when children are asked, “have you used drugs?” they are relatively honest in their responses. On the other hand, if you ask adult athletes, especially elite athletes, even using anonymous surveys, it is exceedingly unlikely they will be forthcoming about their drug use. I realize a scientist should never say never, but I doubt I would ever again conduct a survey of elite athletes, simply because I do not think they are going to tell me the truth! As stated above, doping is covert, it is at odds with social norms, the rules of sport, and the criminal law of some countries. As a result, the data obtained through scientific surveys of elite athletes likely reflect a sizeable underreporting bias and need to be interpreted with great caution.

2.4 Investigations

Thus, we are left with government and journalistic investigations as means to assess the magnitude of the doping problem. In Canada, there was the Dubin Commission, established after the Ben Johnson scandal, and there have been similar government investigations of doping in the United States, France, and Italy, among others. There have also been numerous investigations conducted by journalists over the past five decades. These government and journalistic investigations have detailed sustained, widespread doping in sport at the professional and Olympic levels. Although not without limitations, it is my opinion that the results of these investigations paint a far more accurate picture of the magnitude of the doping problem than do drug tests or scientific surveys. However, while the findings of these investigations are of significant value from a historical and policy standpoint, they are of little use to an epidemiologist in calculating precise incidence and prevalence rates.

2.5 Performance Effects

Another potential contribution of epidemiology in the fight against doping is to determine whether certain drugs are indeed performance enhancing. While there is a consensus on the performance effects of some drugs in...
some sports – such as amphetamines – there are little or no data on the performance effects of other drugs (see tab. 5). For example, even with anabolic steroids – a drug that has been the subject of a numerous scientific investigations – we have yet to determine through scientific study the optimal dosing to achieve the recovery or anti-catabolic effect reported by so many athletes. We have yet to determine the optimal dosing to increase strength and muscle mass. We have yet to determine how long the performance effects last following cessation of drug use, and so on.

As stated previously, the list of banned substances is growing and for a number of drugs on this list we do not have solid scientific information as to whether they do or do not enhance human capacities. In addition, there is little or no financial support to conduct such studies, particularly, expensive random clinical trials (RCT) in humans. As an epidemiologist, the RCT is the gold standard. At this point, I am not as interested in studies showing the performance effects of drugs on rats, hamsters or monkeys. I want to have studies with elite athletes!

Tab. 5: Scientific problems.

<table>
<thead>
<tr>
<th>Effects on performance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Consensus for performance effects of some drugs – amphetamines, anabolic steroids, EPO.</td>
</tr>
<tr>
<td>o For the majority of drugs, the performance effects are unclear – hGH, IGF-1, clenbuterol, bromantan, syndocarb, blood substitutes.</td>
</tr>
<tr>
<td>o Difficult to conduct RCT that mirror use by athletes:</td>
</tr>
<tr>
<td>o Ethics, time, &amp; costs</td>
</tr>
</tbody>
</table>

2.6 Health Effects

Another challenge confronting epidemiologists is to identify the effects of doping on the health of athletes. However, athletes often use doping recipes involving multiple drugs. Moreover, the ingredients of these doping recipes are changing constantly and trying to isolate the health effects of a single drug while the athlete is engaging in polypharmacy is like trying to hit a fast moving target. A few months ago I gave grand rounds at one of our major medical centers attended by some of the top toxicologists in U.S. I asked whether they had heard of such experimental drugs as actovegin, perfluorcarbon, and hydroxyethyl starch – all three had been recently reported by the media as being used by athletes to enhance their performance. None of the physicians had even heard of these drugs! The point is, some athletes are using experimental drugs that are so much on the “cutting edge” that experienced toxicologists did not even know of their existence! Further, I submit that many of the drugs being discussed at this Conference are now considered “obsolete” by athletes. We find out about many of these drugs after athletes and their “scientific” advisors have moved on to something new. What is currently happening in doping is a well-guarded secret and clearly not public information. This further compounds the difficulty of my charge as an epidemiologist – i.e., as the list and combinations of doping agents keep changing, the complexity of identifying the health risks to athletes increases (see tab. 6).

Tab. 6: Performance enhancing drugs (PEDs).

<table>
<thead>
<tr>
<th>PEDs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Cyproterone Acetate o GHB</td>
</tr>
<tr>
<td>o EPO o hGH</td>
</tr>
<tr>
<td>o Perfluorcarbon o Anabolic Steroids</td>
</tr>
<tr>
<td>o Hydroxyethyl Starch o Clonidine</td>
</tr>
<tr>
<td>o Actovegin o Insulin</td>
</tr>
<tr>
<td>o DCLHb o L-dopa</td>
</tr>
<tr>
<td>o RGR-13 o Amphetamines</td>
</tr>
<tr>
<td>o HCG o Clenbuterol</td>
</tr>
<tr>
<td>o GnRH o Bromantan</td>
</tr>
</tbody>
</table>

Setting aside the complexity of isolating the health effects of individual doping agents that are used in combination, we do have some information on the acute effects of a number of the drugs used by athletes. However, much of this information comes from the results of clinical studies. Unfortunately, the subjects in many of these studies are infirm and the studies employ dosing regimens that are often quite different than those used by athletes (see tab. 7). Thus, the applicability of this clinical information to the health of athletes is problematic. Episodic use of doping agents also presents a methodological problem. For example, we know what happens when the body produces excessive growth hormone over long periods of time, i.e., acromegally. However, will an athlete using rhGH in an episodic fashion – 2 eight-week cycles in a year – develop acromegally? What about two years of use? We do not know the answer.

Other information on adverse drug affects is derived from case studies, clinical anecdotes, or accounts in the lay press, the conclusions from which potentially suffer from significant threats to internal and external validity.
Tab. 7: Identifying effects on health.

**PEDs:**
- A long and growing list of PEDs,
- Acute effects are known for some PEDs – mostly from clinical studies,
- Variation of effects within type of PED.
- Athletes use of PEDs at a dose, frequency, and duration often different from clinical applications.
- Long-term effects are generally unknown.
- Difficult to conduct RCT that mirror use by athletes:
  - Ethics, time, & costs.

Another challenge facing the epidemiologist is the significant variation of health effects within drug type. For example, there are substantial differences in the physiologic properties of oral versus injectable anabolic steroids. Of equal or greater importance is the dearth of knowledge of the long-term health effects of most performance enhancing drugs. Again, anabolic steroids serve as a good example. These drugs have been part of the medical armamentarium for over 65 years and they have been used as doping agents for almost that long. However, we have yet to perform a comprehensive epidemiologic investigation of the long-term health effects of anabolic steroids, similar to those studies conducted for tobacco, alcohol, marijuana, etc. (see tab. 8). Even for a supplement as ubiquitous as creatine, we have yet to determine the health consequences of high dose use ten years or more down the road. Furthermore, to conduct such sophisticated longitudinal investigations would take a great deal of time and money. To date, neither government agencies or, in particular sport federations, have been willing to devote substantial resources to such endeavours.

**Tab. 8: Research design – in order of sophistication.**

<table>
<thead>
<tr>
<th>What do we need?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Case studies/ clinical anecdotes</td>
</tr>
<tr>
<td>- Retrospective studies</td>
</tr>
<tr>
<td>- Prospective/ cohort studies</td>
</tr>
<tr>
<td>- Observational</td>
</tr>
<tr>
<td>- True experiments (RCT)</td>
</tr>
<tr>
<td>- Blinded</td>
</tr>
<tr>
<td>- Crossover</td>
</tr>
</tbody>
</table>

Another potential confounder in epidemiologic investigations of the health effects of doping is that athletes come in all sizes, shapes, and colours. In particular, there has been well-deserved criticism that many of the epidemiologic studies of doping agents have tended to focus on white males (see tab. 9). In addition, athletes, even within the same sport, can differ greatly regarding their training regimens and diets. These differences can also serve as potential confounders in studies on doping.

**Tab. 9: Epidemiological problems.**

<table>
<thead>
<tr>
<th>Other Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Individual characteristics:</td>
</tr>
<tr>
<td>- Gender, race, age, training level, skill level, mental state, genetic endowment, etc.</td>
</tr>
<tr>
<td>- Multiple/ concurrent drug use</td>
</tr>
<tr>
<td>- Purity, content, and dosage</td>
</tr>
<tr>
<td>- Varied training regimens &amp; diets</td>
</tr>
<tr>
<td>- Episodic use (acromegaly vs. hGH use)</td>
</tr>
</tbody>
</table>

As I alluded to earlier, another potential confounder is that there is multiple drug use by individual athletes, the effects of which need to be controlled. A tangential issue is the purity and content of drugs and supplements. While I personally believe elite athletes have little or no difficulty obtaining any pure pharmaceutical agent they desire, there are other athletes who take drugs whose content and purity is questionable.

### 2.7 Epidemiologic Triangle

The epidemiological triangle – the dynamic interaction between host, agent, and social environment – can play a major role in understanding the doping pandemic (see fig. 1).
Fig. 1: Impacts the incidence and prevalence of PEDs.

A number of performance enhancing drugs are not euphorogenic or mood altering immediately following administration. Instead, the appetite for these drugs has been created predominantly by our societal fixation on winning and physical appearance. An infant does not innately believe that a muscular physique is desirable – our society teaches this. Likewise, children play games for fun, but society preaches the importance of winning – seemingly, at an increasingly younger age.

Many cultures thrive on competition – both in business and in sport. However, we long ago realized that competition of all types must exist within some boundaries. A primary goal of competition is to win or be the very best in any endeavour. Philosophically, many appear to have taken a “bottom-line” attitude and consider winning the only truly worthwhile goal of competition. If we accept this philosophy, then it becomes easy to justify, or be led to the belief, that one should win at any cost. At that point doping becomes a very rational behaviour, with the end (winning) justifying the means (use of drugs).

Some might argue that attitudes and values related to sports and appearance are too deeply entrenched to change. However, if we cannot control our competitive and narcissistic natures, we then must resign ourselves to performance enhancing drug use, even among our children.

2.8 Conclusions

To date, we have lost the battle against doping. Consequently, if you use the past to predict the future of drug use in sport, I regret to say I am not optimistic. The number of new drugs is growing at a rate beyond the ability of testers to effectively respond; as we close down one loop-hole in drug testing, another opens. Of greater importance is the growing amount of money in the business of sport, providing powerful incentives to athletes, coaches, and sport federation officials to either surreptitiously support doping or, at least look the other way. On the other hand, there has been far too little money directed at research for drug testing. I’m not a chemist, I’m an epidemiologist, but I think sport federations need to invest $100 Million (about 100 million Euros) over the next 5 years to give the top chemists around the world the opportunity to develop tests for the myriad of drugs used by athletes that will stand up to legal challenge. At the end of 5 years, if there is no substantial progress in the fight against doping, we should stop drug testing. But this entire discussion could be moot in that within ten years or less we will likely be faced with the genetic re-engineering of high performance bodies. This will present the testers with far more daunting problems than those faced currently. In the end, we may have to surrender. Let the athletes and their coaches do as they may. While this notion would be unpalatable to many, the stench of 40 years of sport mired in hypocrisy is also distasteful.

In closing, let us return to our social environment and its influence on doping. If I polled the people in this audience and asked: “Are you upset by doping?”, “Are you against doping?” I am certain virtually everyone here would say, “Yes.” However, a far more relevant question is: “Are you upset enough about doping to turn off your television and not watch sports events?”

2.9 References

2.10 Address

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3 Side Effects of Doping: an Overview

Christiane Peters, Thorsten Schulz and Horst Michna

3.1 Introduction

The long death row of elite athletes due to drug abuse stimulated a lot of discussions both in public and politics. Although some high elite athletes confess to have taken doping substances to enhance their physical efficiency, only in a few cases death as a drug abuse consequence could be proven. Within these cases of death due to side effects of drug abuse the former world class athletes R. Reichenbach (shot put) and U. Beyer (throwing the hammer) can be cited. Discussions concerning the unresolved death of Florence Griffith Joyner did not fall silent until now.

Results of the two German IOC accredited laboratories concerning the incidence of positive doping tests in Germany in 1999 could show that up to-date drug abuse is still an issue in high elite sports (see tab. 1).

Tab. 1: Incidence of positive tests in Germany 1999.

<table>
<thead>
<tr>
<th>Prohibited classes of substances:</th>
<th>Human sports (7875)</th>
<th>Equestrian (1513)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Stimulants</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>B. Narcotics</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>C. Anabolic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Anabolic androgenic steroids</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>2. Beta-2 agonists</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>D. Diuretics</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>E. Peptide hormones, mimetics</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>and analogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive tests</td>
<td>0.95 %</td>
<td>2.7 %</td>
</tr>
</tbody>
</table>

From 7875 urine samples taken in human sports 18 contained stimulants, 1 narcotics, 48 anabolic agents and 4 samples were positive due to diuretics. While the prohibited use of anabolic agents, especially anabolic androgenic steroids (AAS) seem to be the main problem in human sports, analytical results of equestrian showed that the leading class of substances within testing procedure was the group of narcotics, followed by stimulants.

Evaluating these results one has to keep in mind that analytical methods to detect peptide hormones like erythropoietin or human growth hormone in urine samples are not established in the IOC accredited laboratories so far, with the consequence that no positive samples could be detected.

3.2 Stimulants

Stimulants belong to the group A of the IOC list of prohibited classes of substances in competitive sports. They influence the central nervous system and cause a reduced tiredness, increased attention and disposition for competitions as well as aggressiveness. Use of stimulants without medical indication and prescription may cause several biomedical side effects (see tab. 2, Wagner 1991 and chapter 4).

Tab. 2: Biomedical side effects of group A.

<table>
<thead>
<tr>
<th>Stimulants:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Increased alertness</td>
</tr>
<tr>
<td>o Insomnia</td>
</tr>
<tr>
<td>o Inhibited judgement</td>
</tr>
<tr>
<td>o Anxiety</td>
</tr>
<tr>
<td>o Possible increased competitiveness and hostility</td>
</tr>
<tr>
<td>o Addiction</td>
</tr>
<tr>
<td>o Reduced fatigue</td>
</tr>
<tr>
<td>o Aggressiveness</td>
</tr>
<tr>
<td>o Tremor</td>
</tr>
<tr>
<td>o Alterations in hemodynamics (increased heart rate and blood pressure)</td>
</tr>
<tr>
<td>o Increased risk of stroke</td>
</tr>
<tr>
<td>o Heart attack, and sudden death</td>
</tr>
</tbody>
</table>

Depending on the amount of consumed drugs, duration of use and sensitivity of the body the mentioned side effects can be found with different dimension of gravity.
While in 1969 the former world class cyclist Eddy Merckx was suspected of doping, it was only in 1988 that he did not deny the use of prohibited drugs during an interview. From the historical point of view the intake of stimulants belongs to the oldest drug abuse delinquencies. Especially in cycling they are known to pertain to the repertoire also of competitive athletes.

3.3 Narcotics

Narcotics are well known drugs in sports and have been on the first IOC doping list in 1967. Although narcotics do not enhance physical performance in sports they are sometimes used by athletes who would not be able to participate in the training or in competitions because of problems or injuries.

Uncontrolled intake may lead to several psychological reactions, reduced pain sensitivity as well as to an inadequate increase of courage during dangerous situations (see tab. 3, Wagner 1991 and chapter 5).

Tab. 3: Biomedical side effects of group B.

<table>
<thead>
<tr>
<th>Narcotics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria</td>
</tr>
<tr>
<td>Psychological stimulation</td>
</tr>
<tr>
<td>Feeling of invincibility</td>
</tr>
<tr>
<td>Increased pain threshold</td>
</tr>
<tr>
<td>Dangerous situations may be perceived as safe</td>
</tr>
<tr>
<td>Physical and psychological dependence</td>
</tr>
<tr>
<td>Narcotic overdose can lead to respiratory depression and death</td>
</tr>
</tbody>
</table>

3.4 Diuretics

In those sport activities in which body weight is crucial the use of diuretics may have a long tradition. In 1998 four members of the Chinese swimming team were tested positive during the world championships in Perth. They used the diuretic substance triamterene in order to reduce their body weight and by this to gain an advantage for the competition or to mask use of other doping substances. Not only in swimming but also in other kinds of sport where body weight classes are used for classifying athletes and producing fair competitions, diuretics are frequently used as well. Because diuretics can not only reduce weight but also enhance muscle profile it is used in body-building as well. Dehydration and electrolyte imbalances are well known health risks accompanied by others (see tab. 4, Wagner 1991 and chapter 5).

Tab. 4: Biomedical side effects of group C.

<table>
<thead>
<tr>
<th>Diuretics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Muscle cramps</td>
</tr>
<tr>
<td>Volume depletion</td>
</tr>
<tr>
<td>Drop in blood pressure</td>
</tr>
<tr>
<td>Severe electrolyte imbalances</td>
</tr>
</tbody>
</table>

3.5 Peptide Hormones, Mimetics and Analogues

In 1989 the class of peptide hormones and glycoproteins were added to the existing IOC doping list. Most important substances in this field are human growth hormone (hGH) and insuline-like growth factor 1 (IGF-1) as well as erythropoietin (EPO). HGH acts by binding itself to a specific receptor which can be found on the surface of all cells of the body. It stimulates the protein synthesis in muscles and by this muscle hypertrophy. HGH leads to a generation of IGF-1 in the liver. Bone growth can be enhanced by hGH and IGF-1 as well as normal body growth. On the one hand reduced hGH levels in children result in dwarfism. On the other hand enhanced levels can lead to inadequate hand and feet growth.

In therapeutic situations of older people it has been studied that the intake of hGH may reverse the aging process (Jorgensen and Christiansen 1993). Biomedical side effects like hypertension, cardiomyopathy and others (see tab. 5; see chapters 6 and 7) were found after not indicated intake of hGH and IGF-1.
Tab. 5: Biomedical side effects of group E.

<table>
<thead>
<tr>
<th>HGH, IGF-1</th>
<th>EPO:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Hypertension</td>
<td>o Hypertension</td>
</tr>
<tr>
<td>o Cardiomyopathy</td>
<td>o Thromboses</td>
</tr>
<tr>
<td>o Respiratory disease</td>
<td>o Pulmonary embolism</td>
</tr>
<tr>
<td>o Diabetes</td>
<td>o Cerebral embolism</td>
</tr>
<tr>
<td>o Abnormal lipid metabolism</td>
<td>o Death</td>
</tr>
<tr>
<td>o Osteoarthritis</td>
<td></td>
</tr>
<tr>
<td>o Increased risk of breast and colorectal cancer</td>
<td></td>
</tr>
</tbody>
</table>

At the beginning it was usual to extract hGH of cadavers. By this the risk of getting an infectious disease like the Creuzfeld Jacob disease was preeminent. In the meanwhile synthetic generation of hGH and IGF-1 is possible but very expensive.

Erythropoietin (EPO) is a glycoprotein and normally regulated by the oxygen offered in the kidneys and liver. Hypoxia enhances the secretion of EPO to enable the body to provide the organs of the body with the necessary oxygen. Application of EPO induces the proliferation and development of the erythrocytes in the bone marrow and leads to an enhancement of erythrocytes in the blood. By this the possibility of oxygen transport to the muscles is increased.

While EPO was developed for anemic people to enhance hematocrit and oxygen transport up to normal rates EPO intake for healthy people increases the viscosity of the blood. Hematocrit values can be enhanced and by this oxygen transport capacity, a reason why EPO is used in endurance sports. Enhanced blood viscosity and high hematocrit values are therefore combined with an increased risk of thrombosis and embolisms (see tab. 5, Vergouwen et al. 1999 and chapter 6).

3.6 Prohibited Methods

Not only substances are used to enhance physical performance in competitions but also innovative methods which were used to enhance the oxygen transport capacity by itself or which can cover for example the EPO induced increase of hematocrit by changing blood viscosity. Therefore, blood doping is used especially in endurance sports to achieve the physiological effects, which are normally the result of hypoxia training at high altitude. A blood sample is taken under normal training conditions to stimulate the hematopoiesis and by this to compensate the reduced amount of oxygen transport capacity. After a few weeks the autologous blood sample is reinjected and an increased physical performance due to the increased oxygen transport capacity can be observed for a small duration of time.

Biomedical side effects associated to blood doping (see tab. 6) are comparable to those already mentioned in relation to EPO abuse.

Tab. 6: Biomedical side effects of prohibited methods.

<table>
<thead>
<tr>
<th>Blood doping: administering artificial oxygen carriers or plasma expanders; pharmacological, chemical and physical manipulation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Transmission of infectious diseases (e.g., viral hepatitis and AIDS)</td>
</tr>
<tr>
<td>o Overload for the circulatory system</td>
</tr>
<tr>
<td>o Blood clots</td>
</tr>
<tr>
<td>o Icterus</td>
</tr>
<tr>
<td>o Tachycardia</td>
</tr>
<tr>
<td>o Anaphylactic reactions (shock)</td>
</tr>
<tr>
<td>o Itching</td>
</tr>
<tr>
<td>o Respiratory arrest</td>
</tr>
</tbody>
</table>

Furthermore, transmission of infectious diseases like viral hepatitis or AIDS are possible. Because the normal values of hemoglobin and hematocrit were exceeded by blood doping, an overload of the circulatory system and an increased risk of blood clots for these athletes was to be taken into account. To protect athletes in endurance sports, some international associations decided to take blood samples before the competition. In these cases they do not have the aim of doping analysis but to measure whether the athletes hematocrit (UCI: ♀ 47 %; ♂ 50 %) or hemoglobin (FIS: ♀ 16,5 g/dl; ♂ 18,5 g/dl) exceed levels, which in combination with the dehydration during long lasting endurance exercise, could be very riskful for the health of these athletes.

To mask the enhanced hematocrit levels either the described prohibited methods or plasma expanders were used. During the 2001 world championship in nordic skiing, Finnish skiers around Jari Isometsä and Janne Immonen were convicted to have taken plasma expanders.
3.7 Class of Prohibited Substances in certain Circumstances

On the IOC doping list there are some substances (alcohol, cannabinoids, local anesthetics, glucocorticoids and beta-receptor blockers) mentioned, which are limited in their allowed usage in competitive sports: depending on specific medical indications the mentioned substances are allowed to be used by competitive athletes. That means for example that inhalation or surface treatment of glucocorticoids are allowed for asthmatic athletes. Interestingly, the percentage of cyclists suffering from asthmatic problems is (not) understandably high. Problems of use or biomedical side effects depend on the amount and duration of treatment as well as on the sensitivity of the individual (see tab. 7).

An example of the use of these substances in sport is the positive detection of marihuana in Ross Rebagliati, winner of the gold medal in the snowboard contest of the Olympic Games in 1998.

Tab. 7: Biomedical side effects of class III substances.

<table>
<thead>
<tr>
<th>Classes of prohibited substances in certain circumstances:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Drug dependence</td>
</tr>
<tr>
<td>o Suppression of the immune system</td>
</tr>
<tr>
<td>o Psychomotor changes</td>
</tr>
<tr>
<td>o Antimotivational syndrome (e.g., loss of ambition)</td>
</tr>
</tbody>
</table>

3.8 Anabolic Agents

Anabolic androgenic steroids (AAS) and $\beta$-2-agonists are summarized under anabolic agents. AAS are synthetical derivates of testosterone which is the male sex hormone. Testosterone is able to induce an anabolic as well as an androgenic effect. While the anabolic effect results in an increase of metabolism the androgenic effect of testosterone leads to the formation of the secondary sex characteristics in men and to a virilisation in women taking high concentrations of testosterone. Furthermore, the secretion of erythropoietin is stimulated by testosterone.

When athletes are taking anabolic steroids one should keep in mind the pharmacological dose of anabolic steroid hormones. As Paracelsus (1493-1541) already explained: “All things are poisonous and nothing is without poison. Only the dose makes a thing unpoisonous.”

While men normally produce 7 mg of testosterone within 24 hours and women only 0,7 mg, daily doses of Detlef Gerstenberg (throwing the hammer) was about 400-fold (2720 mg) and the amount of Heidi Krieger (shot put) was about 40-fold (25 mg).

AAS may show a wide pannel of biomedical side effects for males and females depending on the dose. They are used in competitive high elite sport (Wu 1998) as well as in body-building. In sports where power in combination with a high velocity are necessary to be successful AAS were used to further increase hypertrophy. In endurance sports such as rowing they were helpful in reducing catabol processes.

Not only athletes competing in high elite sports take AAS. Especially in body-building in combination with diuretics AAS are widely used without any medical control. While in high elite sports only a few selective drugs are (ab)used, recreational sports with the aim of fitness especially body-building exhibit a tremendous pannel of different drugs taken in combination to enhance power and muscle profile.

Biomedical side effects of anabolic agents can not only be physical (see chapters 9 and 10) but also psychological ones (see tab. 8 and chapter 8).
Tab. 8: Biomedical side effects of group C substances.

### Anabolic androgenic steroids:

<table>
<thead>
<tr>
<th>Category</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Cardiovascular | - Hypertonia  
   - Negative changes in fat metabolism  
   - Influence on water balance  
   - Hypertrophy of the heart muscle without an enhanced capillary function |
| Hepatic | - Liver dysfunction  
   - Hepatitis  
   - Cancer |
| Endocrine | - Negative influence on several hormones  
   - Acne  
   - Influence on glucose balance  
   - Breast enlargement (gynecomastia) in men  
   - Negative influence on the spermatogenesis, possibly impotence with chronic or repeated use  
   - Testicular shrinkage  
   - Possibly enlargement of prostate gland (?)  
   - Virilisation in women  
     - Masculinization  
     - Abnormal menstrual cycles (suppression of ovarian function and menstruation)  
     - Excessive hair growth on the face and body (hirsutism)  
     - Deepening of the voice |
| Skeletal | - Enhanced tendon ruptures  
   - Premature closure of the growth centers of long bones (in adolescents) which may result in stunted growth |
| Subjective/others | - Increased aggressiveness and sexual appetite, sometimes resulting in aberrant sexual and criminal behaviour  
   - Changes of libido |

### β-2-agonists:

- Possible “repartitioning” or increasing muscle mass while decreasing body fat  
- Nausea  
- Nervousness  
- Increased heart rate and blood pressure  
- Headache  
- Insomnia  
- Tremor

One of the most important risks of AAS intake in relation to cardiovascular diseases is the negative influence on the fat metabolism. Intake of AAS may also affect the endocrine system.

Negative effects on the liver function with an increased risk of liver diseases or cancer are known as well (see fig. 1).

![Liver cysts of a body-builder who had taken AAS and 40 other compounds (kindly provided by Dr. Hans Sachs; Forensic Medicine, Munich/Germany).](image)

Use of anabolic androgenic steroids in younger people may result in an early closure of the epiphysis. Disruption of tendon structures can also be found (see fig. 2).
Special emphasis must be given to the fact that anabolic steroid hormones may extremely harm male reproductive functions (see fig. 3).

### C. Anabolic agents: biomedical side effects

<table>
<thead>
<tr>
<th>1. Anabolic androgenic steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Testicular shrinkage *</td>
</tr>
<tr>
<td>• Reduction of sperm production</td>
</tr>
<tr>
<td>• Loss of libido ?</td>
</tr>
</tbody>
</table>

* Effects may be permanent

Figure 3 illustrates the reactions induced by an artificial application of anabolic steroid hormones: the administration of the anabolic steroid hormone mimics an enhanced level of circulating serum testosterone to the hypothalamus; as a consequence the hypothalamus reduces the synthesis of gonadotropin releasing hormones which forces the pituitary gland to diminish the secretion of luteotrophic hormone. Less occurring luteotrophic hormone reduces testicular activities: the Leydig cells in the testis reduce the production with the final consequence that – testosterone dependent functions – sperm production and libido is reduced. The bodybuilders taking anabolic steroids will finally notice that a testicular shrinkage will obviously appear.

Especially women taking AAS suffer from several biomedical side effects (see chapter 11 and 12). Effects of virilisation including excessive hair growth on the face and body (hirsutism), deepening of the voice, enlargement of the clitoris and acne can be observed. Abnormal menstrual cycles including dysmenorrhoe or amenorrhoe were reported as well. In a few cases long lasting AAS intake was followed by sexual identity disturbances of women. As an example of this problem the former high elite athlete Heidi Krüger from the former GDR finally decided to become male.

β-2-agonists act on the smooth muscles of the bronchial structures, the uterus and the skeletal muscle associated arterial vessels (see tab. 8). Clenbuterol normally used in cattle breeding may enhance muscle hypertrophy in humans as well. The German elite athlete Katrin Krabbe and her sports colleagues used clenbuterol to enhance performance in short distance running.

### 3.9 Drug Abuse in Fitness Sports

There is some epidemiological data available concerning the use of anabolic drugs in high schools in the United States. Results of questionnaires as well as the numerous advertisements on the internet convincingly indicate that drug abuse is a huge issue of the society. Surveys of the US using interviews or questionnaires indicated that about 2-11 % of the asked pupils already have taken drugs, women showing lower percentages than men (see fig. 4).

Results of a small German study showed a frightening picture as well. 24 percent of the requested men admitted to have taken drugs to enhance their physical performance while eight percent of the women agreed to be positive. One has to bear in mind that only about 50 % of the questionnaires were returned and can therefore be considered for statistics. Furthermore, not all kinds of fitness studios were involved in this survey. The so-called
“hardcore studios” provided the largest number. Therefore, these preliminary results should be proven by a general survey including all different kinds of fitness studios.

The use of doping, in particular anabolic steroids: not only a problem in competitive sports

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Country</th>
<th>Sample Size</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckley WE et al.</td>
<td></td>
<td>USA</td>
<td>n = 2403</td>
<td>m 6.6 %</td>
<td></td>
</tr>
<tr>
<td>Johnson MD et al.</td>
<td></td>
<td>USA</td>
<td>n = 853</td>
<td>m 11 %</td>
<td></td>
</tr>
<tr>
<td>Terney R, McLain LG</td>
<td></td>
<td>USA</td>
<td>n = 1028</td>
<td>m 6.5 %</td>
<td>f 2.5 %</td>
</tr>
<tr>
<td>DuRant RH et al.</td>
<td></td>
<td>USA</td>
<td>n = 1085</td>
<td>m 6.5 %</td>
<td>f 1.9 %</td>
</tr>
<tr>
<td>Boos C et al.</td>
<td></td>
<td>Germany</td>
<td>n = 204</td>
<td>m 24 %</td>
<td>f 8 %</td>
</tr>
</tbody>
</table>

Fig. 4: Results of surveys concerning drug abuse in recreational sports.

3.10 Conclusions

The biomedical side effects of doping substances are almost unknown to the public. Most scientific data stems from investigations with animals under standardized situations concerning biomedical side effects of drug abuse. Scientific human studies under standardized conditions would lead to ethical problems and are therefore almost not available. Information regarding athletes and the amount of consumed drugs are mostly not detailed enough and the amount of drugs taken often can not be reconstructed.

Finally, it must be considered that mostly those athletes consuming doping drugs normally take more than only one substance at the same time. In body-building simultaneous use of numerous substances is widely spread. In science nearly nothing is known about the interaction of several doping substances and the resulting risk for health.

From a former top body-builder who died within his 40’s a short part of the “drug history” is presented in table 9.

Tab. 9: Example of drug abuse in body-building.

Interaction of substances leading to death:

- 10-9 weeks before the competition daily:
  - ephedrine, AN 1, captagon, aspirine, valium, clenbuterol
- 8-6 weeks before the competition daily:
  - 2 injects testoviron a 250mg, 1 inject parabolan, 30 tabletts halotestin, 30 tabletts metandienon, 20IE* STH, 20IE* insuline,
- 5-3 weeks before the competition daily:
  - 2 injects parabolan, 2 injects stromba, 30 tabletts halotestin, 50 tabletts stromba, 24IE* STH
- 2-1 weeks before the competition daily:
  - 2 injects masteron, 2 injects stromba, 40 injects halotestin, 80 tabletts stromba, 24 IE* STH, insuline, IGF

The toxic effect of 102 different substances resulted in the death of the female athlete Birgit Dressel due to an anaphylactic shock in 1987.

Because of the comparatively short time period some drugs like the peptide hormones EPO and hGH or IGF-1 are used in high doses to enhance physical performance; the long-term side effects are unknown so far. Furthermore, there is a great lack of knowledge about side effects due to intake of combinations of several substances. In this context scientific data is required within the next years and decades.

3.11 References


3.12 Addresses

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4 Side Effects of Stimulants

Kimmo Kuoppasalmi

4.1 Introduction

The group of stimulants includes several compounds some of which are presented in the table 1. Amphetamines are the prototypical stimulants of a pharmacologically similar class of drugs which also include cocaine. In this article I will concentrate on discussing the side effects of amphetamine derivatives, as well as the side effects of cocaine.

<table>
<thead>
<tr>
<th>Cocaine, amphetamine and some related analogues:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Amphetamine (d,l)</td>
</tr>
<tr>
<td>o Fenfluramine</td>
</tr>
<tr>
<td>o Metamphetamine</td>
</tr>
<tr>
<td>o Propylhexedrine</td>
</tr>
<tr>
<td>o Chlorphentermine</td>
</tr>
<tr>
<td>o Diethylpropion</td>
</tr>
<tr>
<td>o Phenmetrazine</td>
</tr>
<tr>
<td>o Phentramine</td>
</tr>
<tr>
<td>o Methylphenidate</td>
</tr>
<tr>
<td>o Cocaine and related substances</td>
</tr>
<tr>
<td>o Pemoline</td>
</tr>
</tbody>
</table>

Tab. 1: Stimulants.

The use of stimulants has a long history in society as well as in sports. Coca leaves were already used by Incas in Peru. It was also used at the end of the 19th century in the product of Coca–Cola containing approximately 60 mg of cocaine. It was removed at the beginning of the 20th century from the product. Amphetamines have been commonly used by illicit drug users in many European countries for a considerable period. Populations of amphetamine users were common in Europe since the end of the Second World War for example in Finland and in Sweden. At times, the drug has been associated with distinct sub-cultures. Nowadays stimulants are strictly regulated drugs due to the development of abuse and dependence on them.

4.2 Medical Use of Stimulants

Amphetamines gained medical use in the treatment of attention deficit disorders in children and narcolepsy also in adults. Stimulants have also been used in the treatment of depression of elderly people as well as anorectic drug. Use of stimulants to treat depression concerns mainly two groups of patients:

- Patients who have failed to respond to at least two other antidepressants and psychotherapy (therapy-resistant) and who are seriously depressed and
- Patients with serious and usually terminal medical illnesses such as cancer or AIDS who are depressed and too sick to take other kinds of antidepressants.

4.3 Stimulants and Physical Performance

Amphetamines increase the speed of learning of new tasks. Improvements in athletic performance have also been reported. It has been concluded that amphetamines may enhance anaerobic physical performance while having little effect on aerobic performance. It seems that the capacity to tolerate anaerobic metabolism is increased, the mechanism of which, however, is not known. It has been reported that amphetamines are used in sports due to various reasons. For example, American football players use either low doses or higher doses: those involved in accurate passing may take low doses (5-15 mg p.o.) whereas those involved in aggressive defence may take high doses (30-150 mg p.o.). In addition, stimulants may push the user to greater expenditures of energy, resulting in excessive fatigue.

Some studies have shown that cocaine has no beneficial effect on physical performance. Despite these negative results cocaine continues to be abused in sports. It may be that cocaine induces only psychological effects in athletes which may mediate its positive effects on performance. On the other hand, cocaine may have some positive effects in sports with activities of short duration requiring high intensity of energy output such as basketball. The effects associated with its central stimulatory activity could be more important than its effect on peripheral metabolism. It has been proposed that increased arousal and alertness caused by low doses of cocaine may be useful in sports.
4.4 Physical Effects of Amphetamines (and Cocaine)

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 emotion and behaviour both in animals and humans. Stimulants cause euphoria through dopamine nerves. Cocaine also suppresses the activity of the pontine nucleus and the locus ceruleus, and thereby suppresses feelings of fear, anxiety and panic. Chronic amphetamine and cocaine users develop tolerance to euphoria, but only partial tolerance to the cardiovascular effects. Amphetamine (or related substances) or cocaine intoxication causes tachycardia or bradycardia, pupillary dilatation, elevated or lowered blood pressure, perspiration or chills, nausea or vomiting, weight loss, muscular weakness, respiratory depression, chest pain, cardiac arrhythmias, confusion, seizures, dyskinesias, dystonias or even coma (see tab. 2).

Tab. 2: Stimulants.

<table>
<thead>
<tr>
<th>Diagnostic criteria for amphetamine (or cocaine) intoxication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Recent use of amphetamine (or a related substance, e.g. methylphenidate) or cocaine.</td>
</tr>
<tr>
<td>B. Clinically significant maladaptive behaviour or psychological changes (e.g. euphoria or affective blunting; changes in sociability; hypervigilance, interpersonal sensitivity; anxiety, tension, or anger; stereotyped behaviours; impaired judgement or impaired social or occupational functioning) that develop during or shortly after use of amphetamine (or related substances) or cocaine.</td>
</tr>
<tr>
<td>C. Two (or more) of the following developments during or shortly after use of amphetamine (or related substances) or cocaine:</td>
</tr>
<tr>
<td>- Tachycardia or bradycardia</td>
</tr>
<tr>
<td>- Pupillary dilatation</td>
</tr>
<tr>
<td>- Elevated or lowered blood pressure</td>
</tr>
<tr>
<td>- Perspiration or chills</td>
</tr>
<tr>
<td>- Nausea or vomiting</td>
</tr>
<tr>
<td>- Evidence of weight loss</td>
</tr>
<tr>
<td>- Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>- Muscular weakness, respiratory depression, chest pain or cardiac arrhythmias</td>
</tr>
<tr>
<td>- Confusion, seizures, dyskinesias, dystonias or coma</td>
</tr>
<tr>
<td>D. The symptoms are not due to a general medical condition and are not better accounted for another mental disorder.</td>
</tr>
</tbody>
</table>

Amphetamine (or related substances) or cocaine withdrawal causes fatigue, vivid, unpleasant dreams, insomnia or hypersomnia, or increased appetite (see tab. 3).

Tab. 3: Side effects.

<table>
<thead>
<tr>
<th>Diagnostic criteria for amphetamine (or cocaine) withdrawal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cessation of (or reduction in) amphetamine (or a related substances) or cocaine use that has been heavy or prolonged.</td>
</tr>
<tr>
<td>B. Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after criterion A:</td>
</tr>
<tr>
<td>- Fatigue</td>
</tr>
<tr>
<td>- Vivid, unpleasant dreams</td>
</tr>
<tr>
<td>- Insomnia or hypersomnia</td>
</tr>
<tr>
<td>- Increased appetite</td>
</tr>
<tr>
<td>- Psychomotor retardation or agitation</td>
</tr>
<tr>
<td>C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning.</td>
</tr>
<tr>
<td>D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.</td>
</tr>
</tbody>
</table>

4.5 Psychological Effects of Amphetamines (and Cocaine)

When amphetamines are taken in therapeutic doses, most people experience a sensation of enhanced energy and vitality. This feeling may, with repetitive intake of the drug, follow different patterns. Most often, euphoria will develop, usually with a sense of heightened function and perception. The illicit use of amphetamine stems from such effects as a sense of increased energy, intelligence, talkativeness, confidence, endurance and well being.

Adverse psychological effects of amphetamine use may include irritability, aggression combined with violence, low self-esteem, sleep disturbances, severe depression which may lead to suicide, anxiety disorders, paranoid
ideas, paranoid psychosis involving compulsive, repetitive behaviour, and hallucinations. These adverse effects are quite common among chronic users and are associated with high dose or intravenous use.

During high-dose stimulant use, individuals may experience stimulant induced psychosis characterised by delusions, paranoid thinking and stereotyped compulsive behaviour. It is often also combined with aggressive behaviour. Psychosis is induced more commonly by amphetamines than by cocaine, perhaps because it is difficult to maintain high chronic levels of cocaine in the body. Also stimulant-induced psychosis in humans is related to the dose and duration of administration of amphetamines and cocaine rather than psychiatric predisposition.

Amphetamines (or related substances) or cocaine intoxication cause clinically significant maladaptive behavioural or psychological changes presented in table 2. Amphetamines (or related substances) or cocaine withdrawal causes dysphoric mood and psychomotor retardation or agitation (see tab. 3).

4.6 Development of Abuse or Dependence

Realisation of the risk of abuse and of dependence has led to the attitude that there can be an only very restricted place for amphetamines in medicine. The amphetamines have marked psychomotor stimulant activity in addition to their peripheral sympathomimetic actions. The euphoric effect may enhance craving for amphetamine and the repeated reinforcement may lead to conditioned drug responses which may facilitate the development of abuse and dependence (see tab. 4 and 5).

Tab. 4: Drug responses.

Criteria for amphetamine or cocaine abuse:

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following occurring within a 12-month period:
   o Recurrent substance use resulting in a failure to fulfill major role obligations at work, school or home (e.g. repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
   o Recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance).
   o Recurrent substance-related legal problems (e.g. arrests for substance-related disorderly conduct).
   o Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights).
B. The symptoms have never met the criteria for drug dependence for this class of substance.
**Tab. 5: Drug responses.**

<table>
<thead>
<tr>
<th>Criteria for amphetamine or cocaine dependence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at the same time in the same 12-month period:</td>
</tr>
<tr>
<td>A. Tolerance, as defined by either of the following:</td>
</tr>
<tr>
<td>o A need for markedly increased amounts of the substance to achieve intoxication or desired effect.</td>
</tr>
<tr>
<td>o Markedly diminished effect within continued use of the same amount of the substance.</td>
</tr>
<tr>
<td>B. Withdrawal, as manifested by either of the following:</td>
</tr>
<tr>
<td>o The characteristic syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances).</td>
</tr>
<tr>
<td>o The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.</td>
</tr>
<tr>
<td>C. The substance is often taken in larger amounts or over a longer period than was intended.</td>
</tr>
<tr>
<td>D. There is a persistent desire or unsuccessful efforts to cut down or control substance use.</td>
</tr>
<tr>
<td>E. A great deal of time is spent in activities necessary to obtain the substance (e.g. visiting multiple doctors or driving long distances), use the substance or recover from its effects.</td>
</tr>
<tr>
<td>F. Important social, occupational or recreational activities are given up or reduced because of substance use.</td>
</tr>
<tr>
<td>G. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g. current amphetamine or cocaine use despite recognition of drug-induced depression).</td>
</tr>
</tbody>
</table>

Progression to severe dependence is the exception more than the rule and is highly dependent upon individual vulnerability, the circumstances, the setting, the pattern of use and increases in doses to high-dose use. The rewarding effects of amphetamine and cocaine are influenced by the route of administration, because some routes (e.g. smoking, intravenous use) induce more immediate onset of euphoria. The preferred method of self-administering cocaine has been snorting and, more recently, smoking. The effects of snorted cocaine generally occur within 15-20 minutes, whereas the effects of intravenously injected cocaine can be felt within 1 or 2 minutes. A smokable form of cocaine, e.g. crack cocaine, produces its effects within 20 seconds. Amphetamines come in a variety form (e.g. pill, liquid, powder) but are usually taken orally or intravenously. Intra-nasal use of amphetamines may result in perforated nasal septum, chronic rhinitis and loss of the sense of smell. A smokable version of amphetamine derivatives (i.e. methamphetamine or ice) is also available. Because of its long duration of action it can produce euphoria lasting 12-24 hours.

### 4.7 Toxicity of Stimulants

One consequence of chronic exposure to stimulants is toxicity, especially neurotoxicity. Repeated large doses of dextroamphetamine or methamphetamine are associated with decreased tissue concentration of dopamine and serotonin. The occurrence of neurotoxicity may depend on how rapidly high-dosage administration is achieved. The persistence of amphetamine’s neurotoxicity is unclear. Some studies in primates have shown that the damage of dopaminergic neurons caused by methamphetamine may persist as long as up to 3 years. Cocaine has not been shown to produce such a neurotoxicity as methamphetamine.

Amphetamines have been reported to precipitate or exacerbate motor or phonic tics and Tourette’s Syndrome. Pemoline has also been associated with tics.

Fatalities from amphetamine and amphetamine analogues are infrequent. The problem of fatal overdose is greater in episodic high-dose users than in chronic users of stimulants. It may be connected with high-dose abuse of stimulants of unknown quality and quantity. In chronic users fatal overdose is less frequent in part due to the establishment of tolerance to the induced hyperpyrexia and hypertension. Very few individuals have used up to 1-3 g of oral amphetamine per day for years without any signs of overdose. In contrast, toxic overdoses are reported at 100-200 mg doses. Among stimulants toxic overdosing has been best documented for amphetamines and cocaine. Hyperpyrexia, seizures, hypertensive cerebrovascular hemorrhage, ventricular fibrillation, left ventricular failure and complication of intravenous drug use have been reported as causes of death. Approximately one third of deaths after cocaine use are the result of drug intoxication, but two thirds involve traumatic injuries that result from homicide, suicides, traffic accidents and falls. Death from cocaine can occur within 2-3 minutes, suggesting direct cardiac toxicity, fatal arrhythmia and depression of medullary respiratory centers which are common causes of death. Very high doses of amphetamines can cause abnormal
heart rhythms, salivation, convulsions, strokes, overheating, and even coma and death. Sudden death can occur during physical or emotional stress and may result from cardiac dysrhythmias.

Amphetamine induced heat stroke together with cardiac arrest have caused a number of deaths in cyclists. The combination of amphetamine use with physical exercise which causes dehydration and increased body temperature due to exercise as well as due to redistribution of blood flow away from the skin, thus, limiting the cooling effect of the blood and in the past has had fatal consequences for cyclists.

4.8 Cardiovascular Side Effects

Amphetamines can cause palpitations, tachycardia and elevation of blood pressure. In addition, amphetamine use is associated with acute tolerance to subjective effects but not with cardiovascular effects which may expose the individuals to cardiovascular toxicity of amphetamines. Bleeding within the skull is a rare but well-reported complication of amphetamine use. Intracranial hemorrhages have been reported after the ingestion of as few as 2-4 tablets of amphetamine. Chronic oral abuse of dextroamphetamine (or methamphetamine) has led to a chronic cardiomyopathy.

Cocaine has an anaesthetic effect which is based on the competitive blocking of fast sodium channels in nerve cells. Thus, cocaine decreases the rate of depolarisation and amplitude of the action potential, thereby producing cardiac dysrhythmias and sudden death. Cocaine abuse is a risk factor for myocardial ischemia, infarction and dysrhythmias as well as pulmonary oedema, ruptured aortic aneurysm, infectious endocarditis, vascular thrombosis, myocarditis and dilated cardiomyopathy. Acute doses of cocaine suppress myocardial contractility, reduce coronary blood flow, induce electrical abnormalities and increase heart rate and blood pressure. The cause of its effect can be myocardial ischemia. Cocaine induced infarction is one of the most frequent toxic complications of cocaine use.

4.9 Respiratory Side Effects

Cocaine, when smoked, may cause acute respiratory symptoms, chest pain and palpitations. In addition, inhalation injuries, pulmonary hemorrhage or oedema can be observed. Hot cocaine vapours may also cause thermal burns of the respiratory tract. Of the central stimulants aminorex and doxapram have been observed to induce chronic pulmonary hypertension; chlorphentermine, phentermine and phenmetrazine might also have this effect. It is not a common complication and may, however, involve a genetic predisposition. Pulmonary hypertension may be diagnosed a long time after the drug has been taken.

4.10 Gastrointestinal Side Effects

The physical effects of amphetamines include: reduced appetite, weight loss, dry mouth causing ulcers, dental damage secondary to teeth grinding, high doses may cause nausea and vomiting. In high amounts cocaine has an anticholinergic activity, and it can inhibit gastric motility and expose the gastric mucosa to hydrochloric acid for prolonged periods. Thus, cocaine can cause the development of gastroduodenal ulceration and even perforation.

4.11 Systemic, Musculoskeletal and Skin Side Effects

Rhabdomyolysis with myoglobinuria, hyperpyrexia up to 42.8 ℃, disseminated intravascular coagulation have been reported after cocaine or amphetamine use and intravenous administration of phenmetrazine and methamphetamine.

Perivascular infiltration of amphetamines can produce local necrosis, cellulitis, granulomas and abscess formation.

4.12 Other Side Effects

Cocaine has been associated with liver toxicity. Corneal ulcer secondary to smoking crack cocaine has been shown as well as acute iritis has been reported after intranasal use of cocaine. Amphetamines and cocaine can cause spontaneous abortions, prematurity, low birth weight, intrauterine growth retardation, congenital malformations and vascular disruptions during pregnancy.
4.13 References


4.14 Questions

Question: Traditionally amphetamines have been used by cyclists for a long duration. You said that there is no effect. Is there really no effect?

Answer: That’s the message of literature. It can be in contrast to practice as we have already heard. But we know what the meaning of the science is and what the practice is, how the athletes use different drugs. It is very difficult to show that a drug is not effective because you need very big sample sizes.

4.15 Address

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5 Side Effects of Narcotics and Diuretics: Review of Literature
Carl Müller-Platz and Simone Schmidt

5.1 Introduction
Diuretics and narcotics are two of the classes of prohibited substances in high level sports (WADA 2001). In regard to other drugs used in competitive sports narcotics and diuretics are less frequently taken. The misuse of anabolics is still as important today as it has been in the last three decades, other substances attract more and more attention for example peptide hormones like EPO and GH.

The IOC statistics of competition and out-of-competition testing in 1998 and 1999 show that from almost 200 000 samples tested, 1892 proved positive for anabolics, whereas only a tenth, 198 samples were positive for diuretics and only 27 positive for narcotics.

Nevertheless, side effects of diuretics and narcotics can be severe and some remarks have to be made on these matters.

5.2 Methods
The presentation is a literature review and we will give some short explanations of the methods used (see fig. 1).

Two databases were used in this survey, the SpoLit – sports literature data base of the Federal Institute of Sport Science – and the MedLine. Subjects of research were the class names of the prohibited substances, the examples in the list, and the side effects. The research lasted from 1995 up to now.

The further selection was performed by analysing the abstracts. Only articles in English, German and Italian were evaluated.

More than 2000 hits were screened and at least 110 articles have been evaluated. Regarding this method the results of the survey can give only a general view about the side effects of these two prohibited classes of substances enriched with some newer aspects. The aim was also to establish a ranking of side effects as a source for further information to coaches and interested people. The latter group is also important regarding the body-building scene.

It also has to be kept in mind: most articles report on side effects in patients and not healthy volunteers (Eades et al. 1998). The way of application of the drug is different, mostly intravenous, followed by intramuscular and oral, regarding the narcotics also intrathecal. For this reason it was necessary to take notice of the description of side effects and their incidence.

Many articles relate to side effects after long-time therapy. The dosages and chemical formulations varied throughout the articles regarding the same given active substance. Some effects were caused by drug-drug interactions (Lee and Chiou 1998). The findings of such effects have to be further discussed (van Puijenbroek et al. 2000).

The relationship between dosage and side effects including i.m. or oral administration reabsorption rate differs from article to article (Vergin et al. 1998).
5.3 Diuretics

Reasons for the misuse of diuretics in high level sports are:

- To flush previously taken prohibited substances with forced diuresis. This effect was examined by Delbeke and Debackere (1991) who showed that stimulants are washed out. But these substances nevertheless have been tested also after forced diuresis but in a smaller amount. This indicates that the desired effect does not always occur.
- Another desired effect is to lose weight for starting in a lower weight-class in competition.

For these reasons urine samples out-of-competition and in competition are tested on diuretics. The German IOC accredited laboratories have tested about 24,000 urine samples for the German Sports Federation in and out-of-competition during the period 1994-2000. 28 samples were positive on diuretics, 15 of them from only about 200 samples in body-building competition testing. It is therefore remarkable that in body-building it is a desired effect of the use of diuretics that all subcutaneous tissue water will be washed out for a better definition of the muscles. It needs only a short time to find a web site which gives advice regarding the use of diuretics (see fig. 2).

Fig. 2: Possible misuse of diuretics.

The diuretics force the renal excretion. Diuretics can be classified according to their site and mode of action (see fig. 3).

Fig. 3: Classification of diuretics.

Diuretics like mannit and sorbit act through the osmotic pressure caused by the failing possibility of reabsorption from the tubules. Caffeine as other xanthines enhances the blood flow in the kidneys. Most loop diuretics are often used as fast acting substances. They inhibit the active Na/K/Cl-carrier process. Thiazides inhibits the Na/Cl-carrier in the distal tubulus. Also aldosterone-antagonists mask the water-keeping effect of aldosterone by competitive blocking of the responsible receptors in the distal tubule. The therapeutic use of diuretics is considerable safe, perhaps different reaction-patterns occur in male and female (Franson et al. 1997).
Many side effects can be described along their mode of action and the possible imbalances of electrolytes. An insulin-intolerance will perhaps develop, corresponding with the enhanced glucose excretion (Fuster et al. 1998). Other effects (Fowler and Murray 1995, Silverberg et al. 1995, Pope et al. 1996) are also described. Fuster and colleagues (1998) reported a rise in cholesterol and triglyceride levels caused by a hydroxysteroid-dehydrogenase inhibition. This is also reported by other authors. Flack and Cushman (1996) showed a table with the most frequent side effects of hydrochlorothiazide. Headache was the most frequent side effect, followed by drowsiness and fatigue. Sinusitis is a further but rare side effect. The side effects were observed in patients with high blood pressure, so headache is a common sign.

Fine and colleagues (1995) discussed 15 cases of progressive lung oedema during the first hour after oral application of furosemide. He discussed idiosyncratic action without warning. Gerhards and colleagues (2000) reported a case of fatal allergic reaction after treatment with a sulfonamide-diuretic. Suter and Vetter (2000) described the forced excretion of vitamin B1 after treatment with diuretics. Depletion in thiamin may have a negative effect on heart function. In a review article regarding loop diuretics Eades and Christensen (1998) described ototoxicity as a special adverse effect, postulating that the diuretics act also on the endocochlear membrane altering the electrical potential. Therefore, we would like to emphasize the following collection of side effects which should be given as information to coaches and the public in general (see fig. 4).

Slight and heavy side effects are related to electrolyte imbalances. Other effects are hypersensitivity and perhaps allergic reactions on skin. A special warning should be marked relating to lung oedema.

Fig. 4: Proposal for information about side effects of diuretics.

Side effects may sometimes induce benefits. Hydrochlorothiazide has a positive effect on calcium intake in bones. It will perhaps delay osteoporosis in elder women (Barry et al. 1997, Sebastian 2000). A side effect of furosemide via inhalation spray is an immediate broncho-dilative effect in exercise-induced asthma (Larramendi et al. 1997, Melo et al. 1997, Tanigaki et al. 1997). The mechanism is not yet understood. The latter side effect may have effects on doping controls.

5.4 Narcotics

During the same period of doping controls as for diuretics, only 3 samples were positive on narcotics. Not included is the rising number of positive cannabinoid-cases.

Reasons for the rare positive samples may be:

- The use of prohibited pain relieving narcotics will be tested only in competition samples.
- The handling with most of the narcotics are restricted by law because of their potential of addiction.
- Central acting analgesics are often prepared as injection solutions.

The mechanisms of action are not fully clear. The main way of action with regard to the anti-nociception and many side effects can be explained by agonistic and antagonistic effects of the drugs on the so-called opioid-receptors in the central nervous system (Mutschler 2001). Opioid-receptors perhaps also exist in other tissues like visceral tissue (Bhounsule et al. 1996). It is also postulated by different authors that the granulocyte’s membrane carries such receptors (Makman et al. 1995).

Agonists of the µ- (Morgan et al. 1999), δ- and κ-receptors (Blake et al. 1997) in the brain, inhibit the action of afferent nerve fibres, which are responsible for pain. Pain will also be masked in the brain by other feelings. Euphoria will also be produced and is most desired by addicts. The receptors have different subgroups and a new σ-receptor (Couture and Debonnel 2001) is still under discussion. Cloning experiments show that the
biochemical findings of different subgroups can be confirmed. The amount of pain-relieving effects are not only related to the receptor ligand action, as inhibition experiments showed. Additional effects such as the opening of the potassium channels (Ocana et al. 1995) in the postsynaptic membrane or the inhibition of the reuptake of serotonin (Codd et al. 1995) have been discussed.

We know of mainly three kinds of narcotics:

- Pure agonists on opioid-receptors (for example morphine, meperidine, methadone),
- Partly agonists on opioid-receptors (buprenorphine),
- Mixed agonists/antagonists on opioid-receptors (pentazocine).

The therapeutic use of narcotics belongs to severe pain. One of the most problematic side effect is addiction. Many semisynthetic and synthetic narcotics also have a considerable potential of addiction. The side effects of narcotics (see fig. 5) can be summarized in:

- Psychological,
- Physical and
- Other effects.

![Side effects of narcotics](image)

**Fig. 5: Narco-analgesics – mechanism of action.**

The psychological effects will be examined by international standardized side effect questionnaires, the Visual Analog Scale (VAS) or Verbal Rating Scale (VRS). The main side effects have also been pointed out in the previous presentation. Side effects are partly discriminated by the receptors. Respiratory depression and addiction are mainly related to µ-receptor action, dysphoria and sedation to κ-receptors. Disturbances in miction are related to µ- and δ-receptors.

As it was mentioned above most of the studies are related to patients. Only a few number of studies involved healthy volunteers. Erjavec and colleagues (2000) reported that in 15 healthy volunteers after treatment with morphine the alertness was diminished by about 50 %, nausea rose markedly, the mood got worse, respiratory depression and miosis occurred. Zacny and colleagues (1998) examined different effects of pentazocine (30 mg/70 kg) and morphine (10 mg/70 kg) in 16 healthy volunteers after intravenous application. Most reported side effects were vomiting, followed by audio- and visual disturbances. In females also a slight respiratory depression was observed. Lotsch and colleagues (1997) reported drowsiness, dizziness and nausea as the main side effects in 20 healthy volunteers after oral application of 50 mg pentazocine. Mather and Meffin (1978) reported side effects of pethidine in healthy volunteers e.g. respiratory depression, lowering of the psychomotoric performance, visual disturbances and nausea in a review article. Walsh and colleagues (1995) treated 17 male narcotics-experienced volunteers with buprenorphine and gave a good survey on subjective assessment of these volunteers, including all the former enumerated side effects and skin itching. Pupilloconstriction (miosis) is also a well known side effect of morphine-like narcotics.

As a minor side effect sweating and obstipation have been reported in several articles. Allergoid reactions like erythema, pruritus and urticaria have also been reported.

Summarizing the frequency of the side effects described throughout all articles in respect to the percentage of incidence in the studied groups the following ranking results can be maintained: nausea, drowsiness, vomiting, skin itching, respiratory depression, sweating, dizziness. It also seems clear that side effects were not only evoked by a receptor mediated action but also by the effect on serotonin reuptake. Effects on skin, muscle and joints have also been reported but mainly after long-lasting misuse. It has been reported in several articles that pethidine after therapeutic use has been misused over a long period of time other people being unaware of the
fact. Polymyositis, myofibrosis, contractures are also side effects as scleroderma and skin fibrosis are. The mechanisms are not well known.

For this reasons we would like to propose a list of the following side effects as an information for coaches and interested people (see fig. 6).

![Side effects of narcotics]

**Psychological**
- Drowsiness
- Nausea
- Mood-changing
- Depression

**Physical**
- Vomiting
- Slight respiratory depression
- Papilloconstriction
- Sweating
- Obstitution

**Others**
- Skin itching
- Skin redness
- Skin irritations

Fig. 6: Proposal for information about side effects of narco-analgesics.

5.5 Summary

In our opinion there is a high risk that abusers may suffer from one of the demonstrated side effects. The information should be plausible for the coaches and athletes and therefore they should appreciate the warnings about the risk of severe but not frequent side effects.

5.6 References


5.7 Questions

Question: What about the misuse of potassium in the body-building scene? I heard that a user had an overdose of potassium last week.

Answer: Usually you deplete in potassium if you use diuretics. Sometimes for this reason the galenics are accompanied by additional potassium and therefore, it could be that the addition of potassium will evoke a reaction of such a side effect. But normally diuretics lead to a higher excretion of potassium.

5.8 Addresses

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6 Beneficial and adverse Effects of Erythropoietin Therapy
Wolfgang Jelkmann

6.1 Introduction
Erythropoiesis counterbalances the permanent destruction of aged red blood cells by macrophages in bone marrow, spleen and liver. The basal rate of the production of red cells may increase up to 10-fold following hemorrhage. Both the basal and the augmented formation of red cells is mediated by the hormone erythropoietin (EPO). Lack of EPO results in anemia. Anemic patients suffer from fatigue, shortness of breath and tachycardia. Severe cases can require transfusion of red cells from blood donors. Transfusion therapy with allogeneic blood components may cause immunologic reactions and infections. In addition, repeated red cell transfusions can lead to iron overload. Therefore, the availability of recombinant human EPO (rhEPO) as an anti-anemic drug has been one of the most important recent progresses in internal medicine. Unfortunately, it has to be regretted, that – at least in Europe – to the public rhEPO is known primarily as a performance enhancing drug misused for doping purposes in endurance sports. It therefore seems necessary in this context to first outline the beneficial effects of rhEPO therapy before turning to the doping problem.

6.2 Physiological Feedback-Circuit of Erythropoiesis
The $O_2$-capacity of the blood is the main determinant of the rate of EPO synthesis in the kidneys and a few other organs (see fig. 1). The concentration of circulating EPO may increase by three orders of magnitude in response to anemia. In bone marrow, EPO inhibits apoptosis of the erythrocytic progenitors and stimulates their proliferation and differentiation. As a result, reticulocytosis becomes apparent 3-4 days following an increase in the plasma EPO level. Since tissue $pO_2$ is the critical determinant of the rate of EPO gene expression, synthesis of the hormone will also be stimulated when the arterial $O_2$ tension is lowered (e.g. at high altitude) or when the $O_2$-affinity of the blood is increased. In addition, some other hormones interfere with the normal $pO_2$-dependent feedback-circuit of erythropoiesis. Thyroid hormones stimulate EPO gene expression, resulting in increased circulating EPO levels in hyperthyroidism. Androgens augment the effect of EPO on erythrocytic progenitors, thus providing an explanation for the normally higher hemoglobin and hematocrit values in males compared to females.

![Fig. 1: Physiological feedback-circuit of erythropoiesis.](image)

6.3 EPO Therapy
There is a dependence of the serum EPO concentration on the blood hemoglobin concentration in humans with normal kidney function and in patients suffering from chronic renal failure (see fig. 2). Normally, there is an exponential increase in the plasma EPO level when the blood hemoglobin concentration falls below 125 g/l. Insufficient EPO production is the primary cause of the anemia in chronic renal failure. RhEPO was introduced as an anti-anemic drug for treatment of patients suffering from chronic renal failure 15 years ago. Given
intravenously or subcutaneously it is now routinely used to prevent anemia in patients on hemodialysis or ambulatory peritoneal dialysis, as well as in predialysis patients.

![Graph showing serum erythropoietin concentration in non-renal vs. renal anemia.](image)

**Fig. 2:** Serum erythropoietin concentration in non-renal vs. renal anemia.

In this context the recall of the initial dose-response studies carried out in Canada in 1987 is necessary.

![Graph showing dose response to rhEPO therapy.](image)

**Fig. 3:** Dose response to rhEPO therapy.

Having in mind the misuse of rhEPO for doping purposes, it is important to know that relatively low doses of the drug (3 x 15 U/kg body weight) proved sufficient to increase hematocrit significantly. RhEPO can correct the anemia in practically all patients with renal failure, provided sufficient iron is supplemented (see fig. 3).

Understandingly, the number of patients and doctors who wish to avoid allogeneic blood transfusions has increased, since rhEPO has become available for therapy. The value of the drug has been investigated in many non-renal types of anemia with some potential indications. In several countries, the drug has already been approved for treatment of the anemias associated with cancer, AIDS, bone marrow transplantation, myelodysplastic syndromes and autoimmune diseases (see fig. 4).

![Graph showing rates of EPO deficiency and positive response to rhEPO therapy in various types of anemias.](image)

**Fig. 4:** Rates of EPO deficiency and positive response to rhEPO therapy in various types of anemias.
Contrasting the high response rate in renal anemia, rhEPO resistance (hemoglobin increase < 10 g/l in 4 weeks) is relatively often seen in this diverse population of patients. In addition, higher rhEPO doses are usually required for correction of non-renal anemias.

Figure 5 summarizes the beneficial and adverse effects of rhEPO therapy in anemic patients.

<table>
<thead>
<tr>
<th>Beneficial and adverse effects of rhEPO therapy in anemic patients</th>
</tr>
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<tbody>
<tr>
<td><strong>Beneficial</strong>:</td>
</tr>
<tr>
<td>Stimulation of erythropoiesis (increase in peripheral hemoglobin and red cell concentration)</td>
</tr>
<tr>
<td>Elimination of allogeneic red cell transfusion</td>
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<tr>
<td>Increase in physical exercise tolerance</td>
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<tr>
<td>Prevention of anemia-induced hyperdynamic cardiac state</td>
</tr>
<tr>
<td>Improvement of cognitive and psychosomatic functions of the brain</td>
</tr>
<tr>
<td><strong>Adverse</strong>:</td>
</tr>
<tr>
<td>Increase in blood viscosity and arterial blood pressure</td>
</tr>
</tbody>
</table>

Fig. 5: Beneficial and adverse effects of rhEPO therapy in anemic patients.

The most serious unwanted effect is the development or worsening of arterial hypertension. Arterial blood pressure may increase due to the elevated blood viscosity and the loss of hypoxia-induced vasodilation. Of interest is, that most of the patients with non-renal anemia and healthy subjects do not develop hypertension on rhEPO administration, when blood pressure is measured at rest. On submaximal exercise, however, the systolic blood pressure may be higher than before rhEPO treatment, while heart rates are lowered. This observation indicates an improved physical exercise capacity at higher hematocrits.

Erythrocytosis increases the risk to acquire myocardial infarction and stroke. Recently, we have studied effects of chronic erythrocytosis on cardiovascular functions in experimental mice transgenic for EPO. Compared to wild-type mice (hematocrit 0.47), the transgenic animals (hematocrit 0.80) developed left and right ventricular hypertrophy and cardiac oedema. Their life expectancy was greatly reduced as shown in the Kaplan-Meier-plot of survival (see fig. 6).

Fig. 6: Kaplan-Meier plot of survival of erythrocytotic (EPO-transgene) mice vs. normals (wildtype).

### 6.4 RhEPO Abuse in Sports

Since rhEPO became available as an erythropoiesis-stimulating drug, it has been imputed to be abused by athletes in aerobic sports (see fig. 7). In fact, there is suspicion that rhEPO-induced erythrocytosis caused the deaths of about 20 world-class Dutch and Belgian cyclists, although it was never proven that any of these received rhEPO. As noted earlier, however, blood viscosity and, hence, cardiac afterload will increase, when hematocrit exceeds 0.50. In microvessels blood stasis may occur. The main risks of erythrocytosis with hematocrits (het) > 0.55 include heart failure, myocardial infarction, seizures, peripheral thromboembolic events and pulmonary embolism. Endurance athletes are at increased risk during the competition, if their blood viscosity increases further due to the great loss of fluid associated with sweating. Interestingly, the deaths allegedly caused by rhEPO have not occurred during exercise but during periods of physical inactivity.
In endurance sports – such as long-distance running, cycling and skiing – performance relies on an adequate O₂-supply to the heart and the skeletal muscles. Hence, the rate of maximal O₂-uptake is an important determinant of aerobic physical power. The maximal O₂-uptake correlates with the O₂-carrying capacity of the blood.

Thus, within certain limits, an increase in the blood hemoglobin concentration will lead to an improved performance. Other parameters are known to determine the endurance capacity (see fig. 8).

A legal method to increase red cell mass and thereby to improve performance is living at high altitude (and training at altitude or at sea level). Ethically more questionable, high altitude residence is sometimes mimicked by living in tents with reduced O₂-concentration.

Apart from rhEPO doping, ways clearly outside of ethical medical practice are the transfusion of red cells, hemoglobin or artificial O₂-carriers (see fig. 9).

As the past demonstrates, it has been established for decades that an increase in the O₂-capacity of blood may lead to an improved physical performance (see fig. 10). More recent studies have proven the performance enhancing effect of rhEPO doping.
According to Buick et al. (J. Appl. Physiol. 48: 636-642, 1980)

VO$_2$ max (l x min$^{-1}$)

Autologous retransfusion of 900 ml blood increases:

\[ \text{[Hb]} \text{ (from 151 to 163 g/l)} \]

Running time to exhaustion

Fig 10: Example of earlier studies proving the efficiency of blood doping.

6.5 Detection of rhEPO Abuse

Different procedures have been proposed for detection of abuse of rhEPO (see fig. 11).

<table>
<thead>
<tr>
<th>Proposed techniques for detection of EPO doping</th>
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<tbody>
<tr>
<td><strong>Indirect</strong></td>
</tr>
<tr>
<td>• Blood: Hb / Hct, MCV, MCH</td>
</tr>
<tr>
<td>• Blood: Reticulocyte parameters</td>
</tr>
<tr>
<td>• Serum: [Soluble transferrin receptors] / [ferritin]</td>
</tr>
<tr>
<td>(Gareau et al.: Nature 1996)</td>
</tr>
<tr>
<td><strong>Direct</strong></td>
</tr>
<tr>
<td>• Serum: EPO level</td>
</tr>
<tr>
<td>(Souillard et al.: Br J Clin Pharmacol 1996)</td>
</tr>
<tr>
<td>• Serum / Blood: Profile of serum EPO and red blood cell parameters</td>
</tr>
<tr>
<td>(Parisotto et al.: Haematologica 2001)</td>
</tr>
<tr>
<td>• Urine / Serum: Electrophoretic demonstration of (rHu-) EPO</td>
</tr>
<tr>
<td>Lasne and de Cauruz: Nature 2000)</td>
</tr>
</tbody>
</table>

Fig. 11: Proposed techniques for detection of EPO doping.

In this speaker's mind, the demonstration of EPO with the typical physical chemical characteristics of the recombinant DNA-derived-drug in urinary or blood specimens of athletes is the most appealing approach. Endogenous EPO is more acidic than rhEPO. Samples should be collected on a random un-announced basis both in and out-of-competition. Other blood variables that have been suggested for monitoring rhEPO doping include serum EPO concentrations > 40 U/l in absence of anemia, increased soluble transferrin-receptor levels in serum, abnormally high levels of hypochromic red cells in absence of iron deficiency, reticulocytosis and high blood hemoglobin values or hematocrit. The diagnostic value of these parameters is limited, however, if the drug is administered at repeated low doses along with iron.

The exclusion from competition of athletes with abnormally high hemoglobin values may be justified on medical prophylactic grounds. By no means, however, is it proof for rhEPO doping, because hemoglobin levels in unmanipulated male subjects can clearly exceed the limits set by sports organisations (see fig. 12). In addition, figure 12 indicates that there is a large variation in the normal level of serum EPO in healthy humans. The detection of EPO doping is further complicated by major inter-laboratory differences in the reference interval for EPO concentrations and the diurnal variation of the endogenous production of the hormone, resulting in nadirs in the morning.
Fig. 12: Serum erythropoietin (EPO) related blood hemoglobin (Hb) concentrations in healthy humans (n=43).

There is recent success in demonstrating rhEPO in human urine by radioimmunoblotting (see fig. 13).

Fig. 13: Radioimmunoblots of commercial rhEPOs and human urine following isoelectric focusing.

However, future problems may arise because alternatives to rhEPO are under development. Along these lines, in June 2001 a new erythropoiesis stimulating protein (NESP) has been approved as an anti-anemic drug on the European Market.

NESP is a hyperglycosylated analogue of EPO which contains 2 novel N-linked sialic acid-containing carbohydrate side chains (see fig. 14).

Fig. 14: Properties of rhEPO (epoetin) and NESP (darbepoetin).

The extra carbohydrates are added in association with the exchange of 5 native amino acids by site-directed mutagenesis at positions which are hidden in pockets of the molecule and irrelevant for its tertiary structure. The carbohydrate portion of NESP amounts to 52% resulting in an increased molecular mass. Furthermore, NESP is characterized by a lower isoelectric point compared to rhEPO. The mean terminal half-life after intravenous administration of NESP is 3-fold longer than that of rhEPO (25 h vs. 8 h). The availability of rhEPO analogues with different electrophoretic properties, and the possibility of injecting these products in combination, may hinder from detection of EPO doping by analysis of serum and urine species from endurance athletes. Furthermore, in view of the fact that rhEPO and its analogues can be produced by routine molecular biology techniques, the possibility exists that EPO preparations are available from a black market outside from
the established pharmaceutical scene. In any way, generic rhEPO preparations will come to market in the near future, when the present products will no longer be protected by patent.

6.6 Conclusions

The main conclusions concerning beneficial and adverse effects of erythropoietin therapy are:

- The hormone erythropoietin (EPO) regulates the $O_2$-capacity of the blood.
- EPO excess leads to erythrocytosis and EPO deficiency to anemia.
- Erythrocytosis (hct > 0.55) results in an increased cardiac afterload with a high risk of cardiac insufficiency and infarct as well as to an enhanced blood viscosity leading to a disturbance of microcirculation and thrombosis.
- RhEPO doping is not only unethical and illegal, but potentially dangerous.

It has to be added that meetings like the present ones (“Doping: Biomedical Side Effects”, Cologne, July 2001) are of major importance, because information and education of physicians, sports managers, coaches and athletes themselves regarding the ethical but also medical problems that are inherent to rhEPO abuse must be considered the best way to a solution of the problem.

6.7 References


6.8 Questions

Question: Can athletes in the Tour de France finish using EPO two weeks before the tour and then have adequate red blood cells throughout the tour or do they need to continue to utilise it?
Answer: No, they don’t: the life time of red blood cells is about 120 days.

Question: In athletes with normal hematocrit levels, is there any positive correlation between the level of erythropoietin and aerobic capacity (VO₂max)?
Answer: I don’t think that you can establish such a correlation in view of the large variation in the plasma erythropoietin concentration in normal persons even over a wide range of hemoglobin concentration. You may even have seen that there is no difference in the plasma erythropoietin concentration between normal males and females despite the difference in blood hemoglobin concentration. And there you will have a difference in maximum oxygen uptake for sure.

Question: Do you think it’s justified to exclude those cyclists from the Tour de France who’s haemoglobin values exceed 18.5 d/cl?
Answer: It is maybe justified for medical reasons. It is not proved that those who have high hematocrit or hemoglobin values have taken erythropoietin. Especially regarding cycling due to transpiring the cyclists will loose fluid and thus have higher hemoconcentration.

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7 Side Effects of Doping with Growth Hormone

Martin Bidlingmaier, Zida Wu and Christian J. Strasburger

7.1 Introduction

Growth hormone (GH) has gained increasing popularity amongst athletes as a performance enhancing drug. In contrast to many underground rumours, which report a tremendous benefit of GH combined with negligible side effects, we want to highlight the pleiotropic action of GH in the human body. Together with the experience obtained from patients with chronic endogenous GH excess as a consequence of a somatotroph pituitary adenoma, the variety of targets of GH action make it very likely that serious side effects from GH abuse are to be expected.

Growth hormone, which is secreted throughout the whole life mainly by the pituitary gland, acts through the specific growth hormone receptor. The growth hormone receptor is expressed in almost all tissues of the human body (see fig. 1).

Furthermore, growth hormone activates several tissues and pronouncedly liver cells to produce insulin-like growth-factor 1 (IGF-1), which mediates a series of the effects of GH through the IGF-1 receptor. Like the GH receptor, IGF-1 receptors are present in a wide variety of cell types (Le Roith et al. 2001). Therefore, it is not surprising that diverse physiological effects of growth hormone are described for a wide spectrum of different target tissues.

7.2 Clinical Experience

Of course, the effect of promoting longitudinal growth in children is one of the most prominent features of GH action. However, GH effects on bone and cartilage metabolism are omnipresent in adult life as well (see tab. 1).

<table>
<thead>
<tr>
<th>Signs and symptoms in adults:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Enlargement of</td>
</tr>
<tr>
<td>o Hands and feet</td>
</tr>
<tr>
<td>o Nose, chin, tongue and ears</td>
</tr>
<tr>
<td>o Organs: heart, liver, bowel</td>
</tr>
<tr>
<td>o Headache</td>
</tr>
<tr>
<td>o Soft tissue swelling (water retention)</td>
</tr>
<tr>
<td>o Excessive perspiration</td>
</tr>
<tr>
<td>o Fatigue/ weakness of muscles</td>
</tr>
<tr>
<td>o Joint pain (arthralgia)</td>
</tr>
</tbody>
</table>

These effects on bone and cartilage at least in part explain the visible changes associated with acromegaly, a disease caused by a growth hormone secreting tumour and associated with chronic GH excess: Growth of the chin, the nose, the ears and of hands and feet. As an early side effect of GH abuse or GH excess, joint pain due to water retention can occur. Later, the swelling of soft tissue will lead to nerve compression, associated with
paraesthesia and carpal tunnel like syndromes. Long-term GH excess can be associated with joint destruction and arthralgia, a problem frequently observed in acromegalic patients.

Furthermore, GH has profound effects on fat metabolism, on muscle cell growth and on the distribution of fat mass and muscle mass. This becomes evident when looking at data obtained from GH treatment of GH deficient patients: prior to treatment, these patients have an increased body mass index, characterized by an increased fat mass and a reduction in muscle mass.

GH treatment leads to an increase in muscle mass and a decrease in fat mass. However, it has to be mentioned that muscles in acromegalic patients are large, but weak.

In general, growth hormone counteracts the effects of insulin on glucose and lipid metabolism. The effect on glucose metabolism is mainly characterized by increased endogenous glucose production, decreased muscle glucose uptake and rising blood glucose levels. Counterbalance of these effects in subjects with an intact insulin secretion leads to hyperinsulinemia. Thus, GH is a diabetogenic hormone, and impaired glucose tolerance is very common amongst patients with chronic GH excess. Furthermore, about 30% of patients with acromegaly develop clinically overt diabetes mellitus (Holdaway and Rajasoorya 1999).

GH is capable of increasing the glomerular filtration rate in the kidney, which also is mediated through IGF-1 (Hirschberg and Adler 1998). Recently, clinical studies have shown a beneficial effect of growth hormone and IGF-1 in patients with renal failure (Hammerman 1999). Additionally, changes in glomerular and tubular function have been described in patients with GH excess.

Another target of GH action is the cardiovascular system: cardiac function of patients with GH deficiency can be improved by GH replacement. However, many patients with chronic GH excess (acromegaly) develop cardiomyopathy. It is characterized by myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration and areas of monocyte necrosis and results in biventricular concentric hypertrophy. In addition, these patients have a higher incidence of arrhythmias. Consequently, the cardiovascular mortality in this group of patients is increased (Colao et al. 2001).

The interference of GH within the immune system is less clear. Preliminary investigations suggest a role for GH as an immune modulator, and GH receptors are present on a wide variety of cells within the immune system (Auernhammer and Strasburger 1995). However, the exact role of GH and the possible effects of GH abuse on the immune system remain to be elucidated.

Since the use of GH as a therapeutic drug in several conditions has increased during the last years, concerns have been raised whether GH and/or IGF-1 might play a role in cancer development (Cohen et al. 2000). Experiments have shown that IGF-1 promotes proliferation and inhibits the programmed cell death (Kwandwala et al. 2000). From epidemiological studies it is known, that otherwise healthy subjects with an IGF-1 value in the higher (but still normal) range and an IGF binding protein 3 (IGFBP 3) concentration in the lower normal range are at higher risk to develop prostate, colonic or breast cancer (Chan et al. 1998, Hankinson et al. 1998, Renehan et al. 2001). In addition, the mortality from cancer is increased in acromegalic patients.

From this data it is evident that the misuse of recombinant human growth hormone is associated with a variety of possible detrimental long-term side effects. An increase in the prevalence of cardiac and pulmonary diseases has to be expected as well as disturbances of glucose metabolism, joint destruction and probably cancers amongst athletes using GH at high concentrations over a longer period of time.

Aside from these physiological side effects, it should be mentioned that on the black market, GH preparations produced by extraction of cadaveric pituitary glands are still common. It is well known that these cadaveric preparations are contaminated with other hormones, and that one has to be aware of the risk of transmission of infectious diseases (Jacob-Creutzfeldt, HIV, Hepatitis). Due to the illegal nature of doping, in most cases the athlete will not be able to distinguish between pure, recombinant and cadaveric preparations.

Research to develop a test method for the detection of doping with GH is under way, and promising results have been published. Despite this, it is necessary that physicians, trainers and other people responsible for education in sport are aware of and informed about the serious side effects associated with the uncontrolled use of growth hormone. Growth hormone is a very potent, pleiotropic drug and its use must be limited to scientifically proven, medical indications and controlled clinical trials.

7.3 References

7.4 Questions

Question: A big clinical trial in intensive clinical care patients has shown that anabolic effects caused a doubled mortality relative risk for patients.

Answer: I know this study and it’s a very important hint that we have to be careful with the use of growth hormone. But on the other hand you know that the selection of patients for this study was “random” and therefore, I would like to distinguish between clinical use in controlled situations in certain patients and this uncontrolled use of growth hormone in anti aging, in sports.

Question: During each exercise bout the growth hormone largely increases. What is the difference to doping?

Answer: The difference to doping is that the concentration you can reach during an exercise bout is always below 3-5% of your daily secretion rate and the increase you get with additional recombinant growth hormone is much higher.

7.5 Address

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8 Cardiac Side Effects of Anabolics

Asterios Deligiannis

8.1 Introduction

Athletes have been taking drugs or other substances in the hope of enhancing mainly their physical performance, since thousands of years. The use of anabolic agents has become widespread, particularly in body-builders, weight-lifters, power-lifters, and throwers in track and field sports. Prior studies in both human cases and experimental models have observed conflicting effects of anabolics on work performance (Madena-Pyrgaki et al. 1978, Alen et al. 1984). However, the American College of Sports Medicine (1984) has accepted that “the gains in muscular strength achieved through high intensity exercise and proper diet can be increased by the use of anabolic/ androgen steroids in some individuals”.

Several diseases, including cardiac and liver diseases, tumors, as well as other disorders (see tab. 1) occur in athletes who self-administer high doses of androgens. Unfortunately, many “well-established” disorders were based on case reports, anecdotal experiences and misinterpreted studies only in athletes.

Tab. 1: ASS associated diseases.

<table>
<thead>
<tr>
<th>Side effects of anabolics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o  Cardiovascular disorders</td>
</tr>
<tr>
<td>o  Blood clotting</td>
</tr>
<tr>
<td>o  Liver problems</td>
</tr>
<tr>
<td>o  Sexual side effects</td>
</tr>
<tr>
<td>o  Negative effects on libido</td>
</tr>
<tr>
<td>o  Gynecomastia</td>
</tr>
<tr>
<td>o  Tendon damage</td>
</tr>
<tr>
<td>o  Blood glucose regulation</td>
</tr>
<tr>
<td>o  Psychiatric side effects</td>
</tr>
<tr>
<td>o  Behavioural side effects</td>
</tr>
</tbody>
</table>

Myocardial infarction and sudden cardiac death were reported as the most dramatic cardiovascular manifestations in athletes who had taken massive amounts of anabolic steroids (see tab. 2).

Tab. 2: Case reports.

<table>
<thead>
<tr>
<th>Case reports of athletes, who had used anabolics and had a myocardial infarction:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o  22 years old weight-lifter (McNutt et al. 1988)</td>
</tr>
<tr>
<td>o  30 years old weight-lifter (Luke et al. 1991)</td>
</tr>
<tr>
<td>o  37 years old weight-lifter (Faenchick et al. 1992)</td>
</tr>
<tr>
<td>o  28 years old body-builder (Huie 1994)</td>
</tr>
<tr>
<td>o  31 years old body-builder (Appleby et al. 1994)</td>
</tr>
<tr>
<td>o  20 years old body-builder (Dickerman et al. 1995)</td>
</tr>
<tr>
<td>o  23 years old body-builder (Hausmann et al. 1998)</td>
</tr>
<tr>
<td>o  28 years old body-builder (Madea and Grellner 1998)</td>
</tr>
<tr>
<td>o  32 years old body-builder (Fineschi et al. 2001)</td>
</tr>
<tr>
<td>o  29 years old body-builder (Fineschi et al. 2001)</td>
</tr>
</tbody>
</table>

Melchert and Welder (1995) demonstrated four hypothetical models of anabolic-induced adverse cardiovascular effects:

- The first is an “atherogenic” model involving the effects of anabolics on lipoprotein concentrations in serum,
- The second is a “thrombogenic” model, involving the effects of anabolics on clotting factors and platelets,
- The third is a “vasospasm” model, involving the effects of anabolics on the vascular nitric oxide system mainly, and
- The fourth is a “direct myocardial injury” model, involving the effects of anabolics on individual myocardial cells.
8.2 Effects of Anabolics on Lipoprotein Profile

Anabolic steroids have been shown to elevate serum levels of low density lipoprotein (LDL), cholesterol and triglyceride by 40-50% and to reduce high density lipoprotein (HDL) by 50-60% in body-builders and other power-training athletes (Friedl 1993). Perhaps the combined effect of anabolics, weight training and dietary modifications has a more significantly influence on the lipoprotein profile. The reduction in HDL is due to a stimulation of hepatic triglyceride lipase, that regulates serum lipids, by 17-alkylated androgens mainly (Friedl 1993). It is well known that reduced HDL levels as well as other lipoprotein disorders are associated with atherosclerosis, although no epidemiological study on athletes has been reported. Moreover, it was suggested that the increase in total cholesterol by the use of anabolics enhanced the coronary artery response to catecholamines (see tab. 3 and Kennedy and Lawrence 1993).

Tab. 3: Effects of AAS on lipoprotein profile.

<table>
<thead>
<tr>
<th>Lipoprotein levels altered by androgens, thus increasing the risk of coronary heart disease, myocardial infarction and sudden death:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ HDL – Cholesterol</td>
</tr>
<tr>
<td>- 54% in power athletes (Alen et al. 1984)</td>
</tr>
<tr>
<td>- 49% in body-builders (Lenders et al. 1988)</td>
</tr>
<tr>
<td>- 57% in body-builders NS in LDL (Sader et al. 2001)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>- 596 mg/dl in weight-lifters (Mc Nutt et al. 1988)</td>
</tr>
<tr>
<td>▼ LDLC</td>
</tr>
<tr>
<td>- 45% in body-builders (Lenders et al. 1988)</td>
</tr>
<tr>
<td>▼ Apoprotein A - 1/B ratio</td>
</tr>
<tr>
<td>- in body-builders (Lenders et al. 1988)</td>
</tr>
<tr>
<td>▼ Triglyceride</td>
</tr>
<tr>
<td>- 40% in body-builders (Dickermann et al. 1997)</td>
</tr>
</tbody>
</table>

8.3 Thrombogenesis and Anabolics

Recently, Nieminen and colleagues (1996) demonstrated that some possible mechanisms that cause arterial thrombosis by the use of anabolics included increase of several procoagulant factors, platelet aggregation, endothelium release, proteins C and S and also a decrease of fibrinolytic activity and synthesis of prostacyclin (see tab. 4).

Tab. 4: Thrombogenesis and anabolics.

<table>
<thead>
<tr>
<th>Possible mechanisms for arterial thrombosis by ASS (Nieminen et al. 1996):</th>
</tr>
</thead>
<tbody>
<tr>
<td>▲ Several procoagulant factors</td>
</tr>
<tr>
<td>▼ Fibrinolytic activity</td>
</tr>
<tr>
<td>▲ Platelet aggregation</td>
</tr>
<tr>
<td>▼ Synthesis of prostacyclin</td>
</tr>
<tr>
<td>▲ Endothelium release</td>
</tr>
<tr>
<td>▲ Heparin cofactor II</td>
</tr>
<tr>
<td>▲ Protein C</td>
</tr>
<tr>
<td>▲ Protein S</td>
</tr>
</tbody>
</table>

8.4 Coronary Vasoconstrictor Effects of Anabolics

It was hypothesized that androgens may act by receptor-dependent and -independent mechanisms in the cardiovascular system, causing coronary artery spasm (Mc Credic 1998). As mentioned previously, testosterone increases the vascular response to norepinephrine (Kennedy and Lawrence 1993). Also, androgens may be pro-atherogenic, promoting cell adhesion (Mc Crohon et al. 2000). More recently, Sader and colleagues (2001) indicated that the use of anabolic steroids was associated with impaired vascular reactivity, but not with arterial thickening or endothelial dysfunction.

8.5 Direct Myocardial Injury

Some clinicopathologic and experimental studies demonstrated that the intake of anabolic steroids has been associated by marked hypertrophy in myocardial cells, extensive regional fibrosis and necrosis, increased fibrous, as collagen and decreased elastic proteins in the coronary arterial wall (Behrendt and Boffin 1977, Luke et al. 1991, Hausmann et al. 1998). The cellular modifications include both changes in the contractile apparatus,
Moreover, oedema may be induced, while the extracellular space is occupied by a large number of collagen fibrils (Hausmann et al. 1998). Similar myocardial alterations are known to occur in early stages of heart failure.

8.6 Effects of Anabolics on Left Ventricular (LV) Structure and Function

There is evidence that anabolic steroids have a direct effect on LV remodeling, in addition to the effects of training, but whether this is of pathological significance is unclear. It was stated that anabolics cause an increase in LV size and mass, which was independent of total body mass increase (Urhausen et al. 1989) and that cardiac remodeling was associated mainly by increase in diastolic stiffness and impairment of diastolic properties in experimental studies (Appell et al. 1983). Urhausen and colleagues reported that early diastolic function measured by the isovolumetric relaxation time was longer in athletes using anabolics than in the non-users, while systolic function did not differ (Urhausen et al. 1989). On the contrary, some clinical studies fail to document differences in cardiac morphology and function between athletes who do or do not use anabolic steroids (Deligiannis et al. 1988, Thompson et al. 1992).

8.7 Anabolics and Dysrhythmias

Several experimental models have demonstrated a variety of mechanisms by which anabolic use can generate dysrhythmias. It was supported that anabolic steroids may elevate the levels of sodium, potassium, calcium and phosphate and thereby increase the risk of atrial and ventricular fibrillation (Neumann and Schenck 1987, Sullivan et al. 1999). Also, anabolics were found to cause a deep prolonged depression of the stimulation threshold of the heart (Svorcik and Bicikova 1978). Nieminen and colleagues reported the increased automaticity as the possible electrophysiological mechanism of ventricular fibrillation which was observed in an athlete using anabolic steroids (Nieminen et al. 1976).

8.8 Anabolics and Hypertension

Androgens can theoretically effect blood pressure in some individuals because of sodium and water retention mainly after abuse of steroids (Friedl 1993). However, there is not a well-established influence on blood pressure by long-term anabolic steroid use.

8.9 Conclusion

There is evidence that long-term abuse of anabolic steroids causes cardiotoxic effects in users. Sudden cardiac death, myocardial infarction, cardiomyopathy and severe arrhythmia were reported to be the most dramatic cardiac disorders caused by the use of anabolic steroids. However, more epidemiological data is needed to evaluate the prevalence of morbidity and mortality in users.

8.10 References


8.11 Questions

Question: Do you have any data concerning the effects of steroids on the plaque stability itself or is there any dose dependency demonstrated so far?
Answer: No, I don’t have any resent data but in some athletes they found myocardial infarction with free coronary arteries.

8.12 Address

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9 Anabolic Steroids alter Cardiac Adaptation to Exercise
Wilhelm Bloch

9.1 Introduction

In addition to application in clinical practice, anabolic androgenic steroids (AAS) are abused in sports for the improvement of physical performance and the increase of skeletal muscle mass. Numerous side effects have been reported in connection with anabolic steroids, especially in combination with exercise. Besides different other organs the heart is effected by treatment of anabolic steroids, especially under exercise conditions. Alterations of cellular pathology and organ physiology are described which are similar to those seen with heart failure and cardiomyopathy. Hypertension, ventricular remodelling and dysfunction, myocardial ischemia, sudden cardiac death and higher vulnerability for myocarditis have been temporarily and causally associated with anabolic steroid use in humans (for review Kennedy and Lawrence 1993, Sullivan et al. 1998). These cardiac side effects lead to a significant increase of morbidity and mortality (see fig. 1).

Fig. 1: Cardiac side effects of AAS.

The numerous cardiac diseases occurring under anabolic steroid abuse can be explained by different cellular targets for anabolic steroids in the heart. At least four different targets can be subdivided in the heart which were shown to be effected by anabolic steroid treatment (see fig. 2):

Fig. 2: Different targets in the heart can be effected by anabolic steroids.

1. Different studies show that alterations of the coronary system as coronary vasospasm, thrombus formation and atherosclerosis occur (Schrör et al. 1994, Melchert and Welder 1995). Apart from the macrovascular alterations a decrease of capillary density could also be observed (Tagarakis et al. 2000 a, b).
2. Furthermore, the cardiomyocyte are effected by anabolic steroid treatment with and without additional exercise (Behrendt 1977, Appell et al. 1983).
3. A further cellular target for anabolic hormones is the sympathetic nervous system. Transient depletion and degeneration of sympathetic axon terminals as well as changed reactivity to catecholamines were reported (Hartmann et al. 1990, Greenberg et al. 1974).

Besides cellular changes alterations of the extracellular matrix were found in the heart of athletes who self-administered large amounts of anabolic steroids. Pathological studies from these subject showed generalized and focal fibrosis (Luke et al. 1990, Kennedy and Lawrence 1993).
In the following the influence of anabolic steroids and exercise for cardiomyocyte structure, sympathetic nervous system and capillary density is described in more detail.

### 9.2 Alterations of Cardiomyocyte Size and Structure

In an experimental study on guinea pigs, Appell and colleagues (1983) demonstrated the pathological influence of anabolic steroids in combination with exercise for the cardiomyocyte structure. The structural alterations of cardiomyocytes are myocyte hypertrophy, enlargement of sarcoplasmic reticulum, destruction of mitochondria, aberrant myofibrils and change of myofibril/mitochondria ratio (see fig. 3) (Behrendt 1977, Appell et al. 1983).

![Structural alterations of cardiomyocytes](image)

**Fig. 3: Structural alterations of cardiomyocytes.**

Appell and colleagues (1983) concluded that anabolic steroids and training have a similar effect on the cellular components but have different influences on mitochondrial proliferation and if training and anabolics are combined, the cells are pathologically altered. Furthermore, recent findings give evidence that anabolic steroids induce apoptotic cell death in adult ventricular myocytes (Zaugg et al. 2001) which could be followed by a decrease of contractile cells which are necessary for cardiac contractility.

### 9.3 Transient Depletion and Degeneration of Sympathetic Axon Terminals

The effect of anabolic steroids on the cardiac sympathetic nervous system was shown 15 years ago in an experimental study on mice which compared the influence of testosterone in non-trained and trained mice (Hartmann et al. 1986). In this study it could be demonstrated by visualizing intra-axonal catecholamines in the myocardium that exercise and testosterone lead to a distinct transient depletion of the sympathetic axon terminals which is compensated after 6 weeks (see fig. 4).

![Catecholamine containing nerve fibers](image)

**Fig. 4: Sympathetic axon terminals.**

Morphometric measurement of intraaxonal catecholamines and biochemical measurement of the myocardial noradrenaline content revealed that exercise and testosterone, applied alone, have also an effect on the catecholamine content of the axon terminals but in contrast to exercise and testosterone condition the stimulation of the sympathetic nervous system is directly compensated (see fig. 5).
Apart from the catecholamine storage a strong structural damage of the axon terminal could be investigated. Especially under exercise and testosterone treatment extrusion of axons from cytoplasm and degeneration of axon were seen after 3 weeks. After 6 weeks signs of axon regeneration were visible (see fig. 6).

From these findings it can be concluded that:

- Anabolic steroids as well as exercise lead to a stimulation of the sympathetic nervous system.
- Combined effect of exercise and anabolic steroids causes an overstimulation followed by a transient functional and structural destabilization of the axon terminals.
- The transient destabilization of sympathetic axon terminals could be suggested as a reason for increased vulnerability to ventricular fibrillation.

9.4 Decrease of Capillary Density under Exercise and Anabolic Steroids

Animal experiments document that anabolic steroids combined with muscular exercise increase the heart weight and increase the size of cardiomyocyte (Bauman et al. 1988, Appell et al. 1983). This growth dependent and the exercise dependent increase of oxygen demand of the myocardium must be compensated by an improved oxygen supply. An increased capillarization can lead to such an improvement of the oxygen supply. It has been known for more than fifty years that exercise increases the capillary density in heart and skeletal muscle (Petren 1936). Under consideration of earlier findings which demonstrated that anabolic steroids impair the exercise-induced augmented capillarization in skeletal muscle (Soares and Duarte 1991, Dimauro et al. 1992), the question arises whether anabolic steroids and exercise also abolish the microvascular adaptation of the heart.
Thus, we investigated the alteration of capillary density in mouse heart after combined stimuli of testosterone and other anabolic steroids in comparison to control, exercise alone and anabolic steroids alone after 3 and 6 weeks treatment (see tab. 1).

Tab. 1: Alteration of capillary density in mouse heart.

<table>
<thead>
<tr>
<th>Materials and methods:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Experimental groups of 10 week old female NMRI mice:</td>
</tr>
<tr>
<td>o Untrained control,</td>
</tr>
<tr>
<td>o Exercise without anabolic steroids,</td>
</tr>
<tr>
<td>o Methandienone-non-exercise,</td>
</tr>
<tr>
<td>o Methandienone + exercise,</td>
</tr>
<tr>
<td>o Oral-turinabol + exercise,</td>
</tr>
<tr>
<td>o Testosterone propionate-non-exercised,</td>
</tr>
<tr>
<td>o Testosterone propionate + exercise.</td>
</tr>
<tr>
<td>o Drugs: 3 mg/kg body weight/week.</td>
</tr>
<tr>
<td>o Exercise program: running on a treadmill 5 days/week, 30 min/day.</td>
</tr>
<tr>
<td>o After 6 weeks the mice were sacrificed and perfusion fixated.</td>
</tr>
</tbody>
</table>

The morphological observation on semithin section of ventricular myocardium revealed an increase of the number of capillary cross sections and an increased branching of capillaries, which is recognizable by oblique sections of many capillaries. Testosterone as well as dianabol abolished these changes in the myocardium (see fig. 7).

![Left ventricular myocard](fig7.png)

Fig. 7: Changes in the myocardium.

Additional morphometrical analyses evaluating different parameters point to the assumption that alteration of cardiomyocyte and capillary adaptation (see tab. 2) support the morphological findings.

Tab. 2: Morphometrical analysis.

<table>
<thead>
<tr>
<th>Morphometry of semithin cross sections of left ventricular papillary muscle:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Myocyte minimal diameter,</td>
</tr>
<tr>
<td>o Capillary profiles per tissue area,</td>
</tr>
<tr>
<td>o Capillary density (number of capillaries/mm²),</td>
</tr>
<tr>
<td>o Intercapillary distance (distance between two adjacent capillaries),</td>
</tr>
<tr>
<td>o Number of capillaries around a single myocyte.</td>
</tr>
</tbody>
</table>

According to earlier studies our investigation showed a trend toward hypertrophy after 3 weeks, when compared with the exercise group. This difference becomes significant after 6 weeks. The testosterone and exercise condition also show a trend toward myocyte hypertrophy in comparison with the control group after 3 and 6 weeks while exercise or testosterone alone show no significant difference compared to control (see fig. 8).
To supply an answer whether the myocardial hypertrophy under exercise and testosterone can be compensated by adaptation of the capillary system we measured the capillary density. Exercise, unlike all other regimens, leads to a significant increase in capillary density after 3 and 6 weeks. The striking absence of this increase in the testosterone and exercise groups indicates an abolished capillary adaptation. The decreased capillary density after 6 weeks of testosterone treatment compared to the exercise group hints at an additional exercise independent testosterone effect. Considering the altered myocyte diameter a further parameter which evaluates the adaptation of the capillary bed independent from myocyte diameter the capillaries per myocyte was also investigated. Three weeks exercise induced a trend toward an increased number of capillaries around a single myocyte in comparison with all other conditions. After 6 weeks there were significantly more capillaries around a myocyte in the exercise group than in all other groups (see fig. 9). The progressive suppression of the exercise induced increase in the number of capillaries around a single myocyte, goes hand in hand with the demonstrated decrease of capillary density.

The functional consequence of the decrease of capillary density and capillaries per single myocyte may be the alteration of intercapillary distance which gives information about the oxygenation capacity of the myocardium. Testosterone and exercise exhibit a significantly longer intercapillary distance in comparison with the control value and a trend toward longer intercapillary distance than the exercise group. This increase becomes more evident over 6 weeks and reaches statistical significance compared with the exercise group. The 6 weeks values of the testosterone and exercise and the control group show only a trend toward longer intercapillary distance. Also the treatment of the mice with testosterone and without exercise for 3 weeks, induces a significantly longer intercapillary distance in comparison to the exercise and the control group. After 6 weeks the testosterone group exhibits a significantly longer intercapillary distance than the exercise group as well as a similar trend in comparison with the control value (see fig. 9).
For other anabolic steroids such as dianabol and oral-turinabol, a comparable alteration of myocyte diameter and capillaries around a single myocyte could be found. Both anabolic steroids induce a maladaptation of the capillary bed in combination with exercise (see fig. 10).

Fig. 10: Scientific results.

It can be concluded that anabolic steroids abolish the exercise induced improvement of capillarization. Furthermore, an adequate microvascular adaptation to the cardiomyocyte hypertrophy which occurs under anabolic steroids or exercise condition does not occur when anabolic steroids and exercise are combined. This results in an increase of the intercapillary distance and a subsequent impairment of the oxygenation of the cardiomyocytes (see fig. 11).

Fig. 11: Scientific results.


Fig. 12: Adaptation of the coronary capillaries.
The exercise dependent adaptation can be attributed to angiogenesis, modified capillary architecture (elongation or increased branching of the capillaries) or a combination of these mechanisms (Mall et al. 1990, Hudlicka et al. 1995).

For exercise induced angiogenesis it is suggested that exercise dependent transient hypoxia and further stimuli lead to an increased expression and release of cytokines as VEGF which induce an angiogenesis (Hudlicka and Brown 1996, Deschenes and Ogilvie 1999, Richardson et al. 2000, Gustafsson and Kraus 2001). Although it is shown that steroids can inhibit angiogenesis (Crum et al. 1985, Lansink et al. 1998) it is not known whether anabolic steroids could abolish the exercise induced angiogenesis (see fig. 13). Especially for the coronary capillaries there is only a sparse knowledge about the mechanisms and signal pathways involved in the regulation of the adaptive angiogenesis.

Further studies are needed for investigation of signal pathways involved in angiogenesis during exercise induced adaptation and for investigation of the influence of anabolic steroids. These investigations should include the detection of angiogenic and anti-angiogenic signal pathway molecules and their cellular and subcellular distribution under different experimental conditions as described above. Although the angiogenesis should be investigated directly in vitro and in vivo using new cell biological approaches which allow to study the effect of exercise and anabolic steroids for angiogenesis in cell culture and transgenic animals, with the help of endothelial cell specific expressed vital reporter molecules such as the green fluoresceing protein (GFP)(see fig. 14).

### 9.5 References


9.6 Questions

Question: The angiogenetic effects are they also documented for other tissues like muscular tissue or liver or even in the intestine?
Answer: Yes, specially for the skeletal muscle comparable effects are described. Other tissues are a little bit more complicated, because the angiogenic effects of these drugs strongly depend on the environment and therefore it cannot be directly projected to other tissues.

Question: Do you know if there is a difference in the reaction pattern of the left or right ventricle of the heart?
Answer: We have done the study on the left ventricle as I showed. But it is not as if in the right ventricle the effect is completely different. It is nearly the same.

9.7 Address

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10 Aggression and Anabolic Steroid Hormones: do Anabolic Androgenic Steroids enhance Aggressiveness?

R. Klaus Müller and Carl Müller-Platz

10.1 Introduction

Influences of doping agents on the central nervous system or on the psychic behaviour are usually associated mainly with stimulants or narcotics which are included in the IOC/ WADA doping definition. Other characteristic actions and side effects are certainly dominating in the class I C anabolic agents and in particular for anabolic androgenic steroids.

Nevertheless, enhanced aggressiveness is frequently mentioned in the literature as a more or less typical effect of at least higher dosages and prolonged consumption of anabolic steroids. If so, this side effect would be a considerable additional risk of the misuse of these doping agents from several viewpoints.

Enhanced aggressiveness would mean:

- A higher risk for the immediate partners/ competitors of misusers,
- A considerable danger for their whole surrounding population.

Epidemiological recognition of such a potential influence might be strongly impeded by:

- The relatively small number of top-level athletes on one side compared with
- The difficulty to survey the spare-time sports population especially the many people misusing doping agents outside top-level or even organised sports, as misuse of anabolics is well known but uncontrolled in body-building, fitness centers and even in high schools and colleges.

In so far, it might be indicated to take this potential negative effect into consideration even though it seems not to be really proven, and although some authors doubt it strongly.

But there arises another problem if the mere possibility or suspicion are taken as facts: misuse of anabolics as a presumed cause of violent behaviour, of crimes like rape and murder, is frequently supposed in court trials as an excuse for diminished responsibility in court trials. Therefore, the question is very important also from the forensic standpoint, whether a pharmacological enhancement of aggressiveness by anabolic steroids is significantly proven and can be considered as an actual additional risk of their misuse. If yes, the allegations of anabolics misuse prior to a violent crime have to be accepted following the well known principle “In dubio pro reo” of criminal law.

This has to happen even independently of whether the suggested intake has been proven or not. Because crime trials are frequently held long after the committed crimes, such suggestions have often to be accepted without any objective detection. Only hair analysis can sometimes reveal an actual misuse for a certain time in the past.

If the postulated enhancement of aggressiveness is not really significantly proven and represents a misinterpretation of insignificant studies, the suggestion of diminished responsibility and penal liability will remain a mere excuse. Its consideration in any judgement as a reason for lowering legal sanctions would then wrongly excuse and indirectly support criminal violence against human beings.

10.2 Literature Survey

With this background, we started a literature survey dealing with this question already in 1998 (presented on the international Manfred Donike Workshop in Cologne), in which we described detailed examples from more than 100 papers. Now we have continued our search and gained additional insight after having reviewed more than 200 papers. It must clearly be taken for granted, that details cannot be given here, but have to be strongly summarised, generalised and somewhat simplified.

The conclusions: literature offers a very confusing and controversial view with very little satisfactory, objectively significant value. This has several objective reasons. Really convincing studies have strong impediments in this area and must remain very limited due to ethical resentments. To simplify matters: one cannot imagine a double-blind placebo-controlled study, where statistically sufficient groups are given super doses of anabolics until some of them would commit rape or murder.
On the other hand, the worldwide population of anabolics (mis)users comprises millions of people. Thus violent outbursts caused by anabolic steroids would have indicated the occurrence of incidences as well as a correlation. Therefore, we assume, that the possible connection between anabolics and aggressiveness is restricted to a "weak aggressiveness" like the readiness and eagerness to compete, the feeling of irresistible power and superiority, "elbow-behaviour" etc. Violence to the harm of others seems to be exceptional. If it occurs, then it seems to be caused by complex conditions including the preselection of the studied groups or by preexisting psychic alterations.

The possible categories of studies, already performed and published, can be separated in the following categories (see tab. 1). The interpretation of these categories can be simplified and shortened.

Animal experiments mainly in mice, rats and monkeys have lead to different and even contradicting results, and with their questionable meaning for humans, they can hardly contribute to our aim of an objective, significant answer. The results have revealed measurable effects, but with little simplification no ethologically assessed social behaviour including aggression.

On the other hand, animal experiments give insight on the pharmacological action on the CNS even on a molecular, biochemical level. This provides valuable information, but still does not explain the obviously very remarkable individual differences, probably genetically determined.

Another important limitation: humans control their actions consciously. Therefore, a possible loss of control becomes more important than the mere somatic, "animalistic" action.

When double-blind experimental studies on humans (see tab. 1) are lacking and epidemiological surveys provide no sufficiently reliable information, there remain only the psychological inventories of various types (see tab. 1). Numerous of such studies based on psychological terms cover a wide variety of schedules with several weaknesses.

**Tab. 1: Categories of studies.**

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The first problem consists in the term “aggressiveness” itself, which has to be defined or confined before its enhancement can be recognised and measured. It must not be explained, that this term covers a wide range of behavioural entities reaching from:
Feelings of or opinions about strength, activity, hostility over
Readiness to accept risks,
Dominance versus submission,
Readiness or eagerness to compete through exerted hostility,
Real violence with insulting harm to others health or
With the extreme of murder.

Following recent opinions, the individual understanding (or score) of the category “aggression” can even be shifted by external factors.

Any study on humans can be based only on the inferior part of this scale, so that results about enhanced aggressiveness refer almost exclusively to more relative, weak aspects of aggressiveness. When items such as “driving a motorcar without fastening seat belts” are considered, an enhancement of aggressiveness is certainly less disputable than that of real violence against health and life.

Other studies (e.g. Dabbs 1996) use criteria like “face expression on photographs of winners and losers”, or the unsocial behaviour of Vietnam veterans for the scoring of aggressiveness.

A second item distinguishing between the psychological studies is the statistical basis, – the numbers of included people reaching from one (case reports) to several thousands. A general impression shows, that the conclusions drawn seem the weaker, the more persons have been included. Middleman and colleagues (1995) presented a study on 3054 high school students (mean age 16, 49 % male) and described only a certain “risk behaviour syndrome”.

Bahrke published a survey on about 1 million users of (several) anabolics in the U.S., revealing an extremely small percentage of mental disturbances severe enough to require medical treatment in 1996. In cases of actual misuse unclear influences concerning psychiatric history, penetic susceptibility, environmental and peer influences, and expectation must be considered.

But how compare and summarise reports with so different information content? Therefore, we still look for an objective way to evaluate the real information content of the overwhelming number, but in total rather diffuse and misleading publications.

Quite recently, our application for a research grant aimed at establishing an objective score. For the available published information the application was rejected by a peer board, arguing that this question has long been decided and does not require further investigation.

The most important, if not deciding limitation of the conclusive information of psychological studies on humans in this direction is the unavoidable preselection of the people included. Prisoners, violent offenders, body-builders or even adolescents in general differ in their attitudes and behaviour from the average population and can hardly be considered representative. Who takes anabolics, who is eager to win at every health risk, who wants to look like a superman? Even the readiness to take part in a study applying the administration of anabolics represents a certain preselection.

This in our opinion strongly influences the results of studies on humans, whether pre- or retrospective. At present, from the forensic standpoint, the apparently plausible answer is “yes” to this question. We therefore consider the question still unanswered, whether misuse of anabolic steroids really enhances aggressiveness not in the sense of competitiveness, but in the sense of hostility against health and life.

In this regard the light of proof might easily fit to the aphorism:

“There is an easy answer to every problem, – neat, plausible and wrong”.

10.3 References


10.4 Addresses

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11 Doping in the former GDR

Giselher Spitzer

11.1 Illegal GDR-Structures – from Professionalism to Doping: introduction

East German high-performance sport has attained a higher degree of differentiated organization than all other Western European sport systems, and as a result was only able to create the illusion of keeping up with the growing demands made upon it. Critical studies (Spitzer 1998/2000) had the following results (see tab. 1):

Tab. 1: The GDR sports system.

High level sports – the system:
- (Illegal) social contract: politically dominated professional sport
  - without free access and
  - with life-long employment guarantee.
- Securing “New Blood” through the selection of the top 3%:
  - Overall analysis of the entire East German youth population: approximately 60.000 children were selected for 1.800 “Training Centers”.
  - Rigorous selection of 10.000 athletes yearly: the 2nd promotion level: “Sport Clubs” and “Child and Youth Sport Schools”.
  - About 20% could rise to the 2.000 top athletes: national teams and high-performance training.

First this system developed an (illegal) social contract: politically dominated professional sport without free access and with life-long employment (By the way: all that at the cost of a reduction in the importance of large-scale social sports programs). To reach the political aims the so-called “New Blood” was recruited amongst the top 3%. In the “ethically questionable” procedure of an overall analysis of the entire East German youth population approximately 60.000 children were selected according to scientific criteria. Training took place in the “Training Center” of which there were about 1.800.

Through rigorous selection, the most promising 10.000 athletes were accepted yearly into the 2nd promotion level: they were delegated to “Sport Clubs” and educated in “Child and Youth Sport Schools”. Those who didn’t “keep up” and make it “to the safe side” fell “into a hole”. About 20% of those who belonged to the second circle in the cadre could rise in rank to belong to the 2.000 top athletes of the national teams: to the national teams (circle 1 in the cadre “Kaderkreis 1”) and the 3rd promotion level (high-performance training in the sport club, “Foerderstufe 3”). The result was: restrictive channeling and professionalization, even outside the group of the athletes (see tab. 2).

Tab. 2: The GDR sports system.

High level sports – the system (part 2):
- GDR athletes were exceptionally well-paid civil servants (or soldiers)
  - With guaranteed career and
  - Obligation to withhold information about the day-to-day course of athletic life, including doping.
  - They were forbidden to have any contact with any persons or organizations not affiliated with the government.
- Athletes were victims of a rigorous control
  - By the Secret Service, “Stasi” (about 3.000 volunteers, “IM” = “unofficial supporters”) and
  - By the Socialist Union Party “SED”.
- Restrictive channeling and professionalism:
  - 4.700 professional trainers; expenses today: 500.000.000 German Marks salary.
  - 1.000 medical doctors; 200.000.000 German Marks plus
  - 5.000 administrators and functionaries – 400.000.000 German Marks.
  - Costs for research and doping: unknown.
  - About 1.500 persons were active in “research” or “application” of doping means.
GDR athletes were exceptionally well-paid civil servants with a guaranteed career and the obligation to withhold information about the day-to-day course of athletic life, including doping means. They were furthermore forbidden to have contact with any persons or organizations not affiliated with the government.

In high-performance sport alone, at least 4,700 professional trainers were employed. We can calculate today that at least five hundred million German Marks were paid on salaries. Nearly 1,000 medical doctors in professional sport make another two hundred million German Marks, plus estimated 5,000 administrators and functionaries about four hundred million German Marks. Costs for research and doping cannot be calculated.

A characteristic feature of the day-to-day life of the athlete was the rigorous control of every aspect by the Socialist Union Party and the Secret Service, the “Stasi” with about three thousand volunteers “IM” (IM = volunteers of the state security).

11.2 Doping as Strategy of the State GDR

In politics of the German Democratic Republic (GDR) there was a need for doping. The necessity of full integration of doping into training and competition was a result of ethically questionable new methods abusing pharmacy as part of science and politics. Here some short remarks:

- Since 1963 doping-methods were used in the organized GDR-sports: cycling, soccer, track & field.
- 1964 for the first time (two) women's Olympic gold medals by non-anabolic doping means.
- 1968 Mexico-City: widespread GDR-use of anabolic drugs, ranking number five in the world!
- 1972 Munich: prestige-duel “within the borders of the class-enemy” and ranking number three, while using anabolic pharmacy.
- 1976 Montreal: ranking number 2 and winning most medals in women disciplines.
- 1988 Seoul: secret plans for reaching number 1 in the world!

There were doping-plans for 1992, but 1989 there was a peaceful revolution, which ended the State GDR.

11.3 “Double Cheating” combining Doping and the Individual Decrease in the Urine Sample

About 2,000 athletes were put on drugs yearly, if we sum it up, it makes (estimated) 10,000 victims of doping. 10,000 plus, because there was a lot of doping beneath the central plans. The system was very complex, an example is given: at the Olympics 1980 the astonishing number of 20 gold medals were won by “double cheating”, that means: beside abusing drugs in the training period, there were secret tests of the individual decrease in the urine sample in order to have a negative competition test.

This method, called “Abklingraten” (fading rate) lead to the following maximum: a higher and longer lasting abuse than in other national sport systems (see fig. 1).

*Fig. 1: Practical drug abuse plan.*

![Practical drug abuse plan](image-url)
1980 many medals would have been lost, if there had been a more effective international control:

- **Skiing**: one Olympic gold medal (team),
- **Cycling**: one silver medal,
- **Judo**: three time bronze (three athletes),
- **Swimming**: 10 gold, 7 silver and 2 bronze medals (by 7 athletes),
- **Track & field**: 9 gold, 2 silver and 3 bronze medals (8 athletes).

Summing up these results: 20 East German gold medals and 18 silver or bronze medals would have fallen victim to a more effective international control – only in the 1980 Olympics!

### 11.4 Self control of the Governmental Structures

There was an internal, critical discussion, without stopping doping. But were there new politics after the peaceful revolution?

The “Elite Sport Camp Zinnowitz” on the Baltic Sea island Usedom, had a medical doctor. In January 1990 he wrote to Dr. Hans Modrow, new elected President of the GDR (see fig. 2).

![Fig. 2: Cutting of a letter.](image)

The doctor gave detailed information on the system of organized GDR-doping. Modrow and the Vice Minister of Sports, Prof. Dr. Edelfried Buggel, had to read information about anabolic drugs: about “legal” ones – pharmacy like oral-turinabol® and “illegal” drugs like “STS” (an experimental anabolic drug)(see fig. 3).

![Fig. 3: Drug abuse description.](image)

The doctor even wrote about dangers of doping for health:

“It [the abuse of anabolic drugs; Giselher Spitzer] should work fast, using little money and should be effective – known dangers” for health were accepted”.

But: The letter had no political consequences against doping.

Did the system “know” about health problems? An official GDR-doping manual proves another aspect of GDR-doping: side effects were well known, but kept as a secret (1982).

Doping drugs had (nearly in every case on women, if you ask witnesses) negative effects to health:

- E.g. the speaker of a ball game team gave me the information, that every woman – she had contact with – has now, decades after the end of the career, gynecological problems.
This manual proves, that because of the risks there were limitations on the dosages. But: banning the drugs was not considered, although detailed knowledge was available.

11.5 Secret Risk Methods and Doping Structures

There were secret risk analysis and doping structures in GDR sport and detected side effects and damages were covered up as effectively as possible. Spot checks showed that the damages were considerably higher than had been reported (see fig. 4). The “magic” limit of 20 % in the calculation of the degree of disability for insurance purposes was only rarely exceeded (one percent more in disability would have constituted a category of “serious disability resulting from sport” in the statistical records).

The result is depressing: if we look at the outstanding year 1977 – following a report of the medical chief of the GDR-doping – 17 athletes wanted to retire because of the disability resulting from sport. All 17 were young athletes.

Pro-doping research about decrease of hormone production and virilisation

The manual explained two side effects to male and female:

- “Inhibition of production of sperms as well as gynaecomastia in men”
- “Cycle-anomalies and virilisation in females (if used at high dosage and long-term treatment: partly not reversible”).

Fig. 4: Pro-doping research.

There was not much knowledge about drugs in athletes, because they were given to the athletes without their knowledge. Doping agents and methods were euphemistically referred to and claimed as “supportive medications”. In reality the broad offer covered the spectrum from “classic” stimulants, through the massively abused anabolic steroids (around 10 kg or 2 million tablets a year) to the ethically deplorable administration of cerebral and peptide hormones as well as blood doping and the abuse of growth hormones.

A kind of “mastership”: the highest “scientific planned” dosage was, if I remember rightly, officially more than 11,000 milligrams of oral-turinabol plus multiple injections with pure testosterone and other drugs.

In 1983, the first medically documented use of human growth hormone on an athlete in the GDR took place – without the knowledge of the tested subject, a cyclist!

- As you can see: human experiments were a common adjunct to the “central planning” of a “highly criminal segment” in East German sport. And this group was by no means small: at least 1,500 persons annually (mostly men) were involved in ”research” and ”application”, to a degree overlapping with separate special interests of the terrorist Secret Service.

11.6 Conclusions: Special Aspects of Doping in the GDR

Finally, a few statements should illustrate what was special about doping in the GDR compared to other forms and societies:

- As a rule athletes would be exposed to compulsory doping because of affiliation to cadres and without their active cooperation: only few athletes knew about and actively cooperated with it. Every selected active person in a sport was doped. It was impossible to refuse.
- Compulsory (or mandatory) doping was supervised and financed by the state, de facto without legal restrictions against doping procedures.
- The sport associations’ central doping guidelines and plans even regulated the dosage for individual athletes.
- The Secret Service and the military as well as a political party (SED = Socialist Unity Party of Germany) guaranteed the additional supply of doping drugs beyond central norms; they developed and financed their own methods.
A considerable amount of doping drugs consisted of illegal experimental substances whose side and late effects were not clarified.

Since athletes reached the threshold value while still juniors, they had a long career in doping drug abuse (in technical-compositional kinds of sport, weight-lifting, and swimming beginning already in childhood).

Athletic achievement was considered to be of higher value than the athletes' actual or future state of health.

After the end of a career the health data were falsified without the victims' knowledge.

Summing up the results of this overview there is one important, most simple and most verifiable “lesson”:

| The controlled release of doping drugs does not result in a restriction of doping at a low level, and, all doping procedures harm the athletes' health. |

11.7 References


11.8 Questions

Question: How do we explain the very obvious fact of many winning performances and medal winners from East German athletes? Is it the result of a systematic doping problem?

Answer: I would have a problem with the fact that science should make research about performance enhancement, about the real effect of doping. I never said the medals are caused by doping, because I am not able to decide if doping is so effective as the system thought. Because of the problem of the GDR, about 1,500 people lived on the activity of doping. If they had said it didn’t work, they would have lost their jobs. Personally, I think that there is an increase of performance because we have very detailed data. We have dissertations about these problems as well as on the effects, but of course with positive tendencies concerning the performance enhancement and with negative tendencies about side effects. But its’ a very wide field because there was a screening in science. The East German scientists tried to make experiences with every substance they found or they heard about.

Question: You mentioned that there was a highly scientific background concerning doping in the former GDR. Could you comment more on who the figures behind the “official” doping in the GDR were, how was the science organised, which drugs were used, how were the testing systems?

Answer: In the terminal system of science there were 2 basic fields: one was applied research without basics and with special regard to practice. To monitor the training, to work together with the coaches. The other part is the industry, pharmacy: they had to develop new performance enhancing drugs for the state, for example new anabolic types. So a lot of the doping in the GDR comprised experimental substances not pharmacy. The system worked in a way that there was centrally planned doping for the athletes. It was controlled in order to prevent higher dosages which could have been detected. This was done not to support the athletes but rather to avoid being caught by doping controls. So one basic element of the system was the so-called “Ausreisekontrolle” (departure control) which meant that an anti doping laboratory was abused for making sure that not a too high percentage of prohibited substances or too many anabolics were found in the urine sample during competition controls. A big problem was that sometimes these two fields were mixed. If you look for example at guide lines of use “Anwendungsrichtlinien”, in the bigger group there were drugged athletes and the smaller group was a group of athletes which were drugged too in another way utilising research. Because of the different kinds of doping the scientists had the possibility to compare whether the classical doping was superior to the experimental doping.
11.9 Address

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12  Doping with Children

Giselher Spitzer

12.1  “But we were Children” – Body Damages in Childhood and Youth, caused by GDR-Doping: introduction

“But we were Children” – this sentence from a letter of a female junior of the 80’s reminds us: even if a great number of the (estimated) 10,000 victims were doped as adults, the age of the first “abuse” of doping means went down. In East-German coaching-terms it was called “Erstanwendung” (first but very effective treatment with anabolic drugs) in weight-lifters and female swimmers.

The girl who reported about her sports career, was top class at her discipline for nearly a decade. She belonged to the best 10 of the GDR. She won national championships (but was not allowed to go abroad for political reasons) (Cornelia J., letter 9th of June 2001 to I. G., Berlin).

She was 13 years old when she began with high performance training. When she was 16 she belonged to the Olympic cadres 1984, from 1979 on. We know today, that on this level doping means were used, nevertheless she was not informed. Her coach (Bernd A.) “merely” told her that she had to take more substances and pills, because of the high performance of training:

“You would rape your body if you do not take the substances” (“Du würdest sonst Deinen Körper vergewaltigen”).

She had to stop competition sport whilst belonging to the GDR National Team at the junior level. 1983 the heart muscle problems appeared, even inflammation of different inner organs of her body, problems of the hormonal status and allergy started. Extreme pain and agony were caused by damage of the vertebral column. Today she is not able to work and has retired.

This case study shows typical aspects: the minors were not informed about that kind of medical “treatment”, neither by doctors nor by coaches or functionaries. But we have to think that she is a victim of doping means, of abuse of pharmacy.

The following will deal with “Kinderdoping” (child doping) in more depth – in my opinion “child abuse by doping means”.

Before going into details it must be said that we can see a “doping-caused syndrome” in the sense of damages of the muscles, bones, joints not directly by e.g. anabolic drugs, but as a consequence of the higher ability to load (“Dopingfolgen-Syndrom”). Orthopedic damages were the result of this doping-induced overload.

In one case a doped girl practiced more weight-lifting than doped male athletes.

12.2  First Reports on Side Effects of Doping from historical view

Since the persons responsible for introducing these substances are keeping their silence, it is necessary to refer to written original documents and to interviews with witnesses.

Descriptions of side effects caused by “classical” doping like amphetamines are available since the 60’s, for example in cycling.

As early as 1969 evidence appeared when the head of the athletics department of the Neubrandenburg sport club, submitted the following information in a confidential tape recording: "report on the alleged use of doping with athlete xxx.”

"One of the true reasons is that he made some kind of mistake with his athletes. For example with xxx. He supposedly was given doping tablets in autumn of last year, ... Because of these tablets his entire musculature has hardened so that he is unable to train at the moment. The official medical diagnosis for his training shortfall is: damage to the spinal column.”

This is the first report about loss of the ability to relax after physical performance and/ or the persistence of a high muscle tonus during rest periods.

Since then a big variety of negative effects on athletes health and mind were reported, either often or seldom.
12.3 Side Effects: Reconstructed by the Help of Secret Files and unethical GDR-Research

Known side effects for both, male and female abusers of anabolic steroids were side effects on the skin. A 16-year old girl had to fight against male hair growth. In the last month I found out that a young male was excluded from the cadre because of his skin-problems, in reality side effects of doping.

But there were also dramatic effects on the liver. Very often abnormal increases of serum transaminase were reported, especially at rowing juniors and weight-lifters. This resulted in the above mentioned side effects of several internal organs as well as an increase of the tonus in skeletal muscle, accompanied by high blood pressure.

Changes of the structure of the heart muscle (and liver destruction) were discovered with a 16-year old swimmer from Magdeburg who drowned. The dissection revealed the above mentioned side effects after hours in the water: heart and liver had changed.

The disturbances of the psyche and the behaviour, accompanied by an increase of aggression and some libido changes, were seldomly reported in clear words, but one can “feel” it between the lines. So one coach declared: “the girls get funny” by male hormones. Young lifters had a high increase of sexual impact.

Victims today report on their growing aggression during the phase of doping.

Aspects like mental disorder, psychic and physical dependence or addiction are mainly missing in the material, but it was necessary to cover these aspects. Internal knowledge about that could have been the sudden end of the GDR-system – due to side effects.

Side effects of male junior athletes were testicle-atrophy – not in reports found yet, but proved by research, and gynaecomastia (an enlargement of the male breast to a female size). The reason was the decrease of male hormones caused by giving anabolic drugs from outside (called: “hormone-depression”). A substantial percentage 34 % – of the best lifters had to retire within one year! One adult nearly died because of side effects in the liver.

Although these side effects in men were severe, dramatic side effects regularly appeared in women:

- “Obvious” was hirsutism, growing of a mustache or beard, or male hair growing at the body-trunk.
- “Obvious” was also the deep voice of girls or young ladies.
- Even “obvious” was the male shape of the body. A coach warned his 16-year old athlete that she might be unable to find a husband due to her male appearance after treatment.

The inner organs of the drugged young female athlete were a special problem. Due to the rise of the sexual (steroid) hormones in the liver, an increase of the free testosterone leading to virilisation was the result. Prof. W. W. Franke called it “androgenisation” (Franke 1995). The last consequence was the sex transformation of the shot putter A. K. – he/ she got anabolic drugs as a child by the official coach. Research will show if there were more cases of transsexuals caused by the GDR doping practice. By the way: literature indicates that the sex transforming hormones induce the best result at the age of 12 to 14. And: used for longer than one year it makes the sexual transformation irreversible.

Anyway: the reduction of female breast and severe changes of the menstrual cycle up to a complete blockade (amenorrhoe) were typical and covered up by the secret system.

With regard to hypertrophy of the clitoris no witnesses want to speak out or report on their experiences.

The atrophy of the uterus is a typical side effect in children, it is shown in some files but reported by victims who had contact with independent medical doctors – they advised to leave elite sport, in order to have the chance to develop a “normal” reproduction system.

Even after the end of the doping-induced career strong changes of the ovaries were reported by former victims of anabolic drugs (This list is similar to the side effects, W. W. Franke summed up in 1995 from world wide literature and GDR-files and -research; quoted in the appendix).

Those athletes who were not informed about the abuse (the majority!) but felt the side effects, had to suffer or to leave: we can see a drop out phenomenon caused by doping side effects. For example: a leading gymnast left the GDR because of side effects, he had knowledge on: oral-turinabol and a brain activating hormone, named “B 17” (Oxytocin).
12.4 Numbers and Figures: Qualities of Damage to the Phenotype and to the Germ Line

Since 1972, 2,000 male and female athletes were annually doped in accordance with these central plans, the overwhelming majority without their knowledge or their legal consent. By my estimate, the victims subjected to these assaults on their health and ethical actions number around 10,000.

The destructive physical effects of doping can be determined through research and courts:

- In the case of around 500 officially doped GDR athletes, effects such as cardiac muscle damage and liver damage are to be expected, which I call “damage to the phenotype”. Here is a need for research (it appears that the German Parliament is considering a research program).
- Side effects on the “germ line resulting in fetal handicap” may have been higher than the population average, independent of the degree of steroid abuse: these I have designated as “damage to the genotype”.
- Of the nine witnesses tested for physical disability related to doping who testified in the "Dynamo Trial", one had already been suffering from liver cancer which would have remained undiagnosed but for the court medical examination. If the tumor grows and blocks a blood vessel, the life of this victim of the infamous training “measure” is in danger.
- Approximately 25 % of the anabolic steroids were experimental substances which had not been checked for side effects until the effected athletes made applications for retirement benefits. The effects remain unknown, as these substances have never been tested. The results have not been analysed.
- According to official GDR research, exactly one third of the women and girls suffered from serious gynecological damage. In my interviews with numerous female former athletes I discovered that, on the contrary, such damage had been suffered “by almost every single case”.
- If we take the Olympic motto “citius – altius – fortius” and apply it to this inhumane doping system: doping was practiced “more, longer, and earlier” (especially in the case of women and girls) in East Germany than in any other country.

Looking at GDR-results on side effects: interpretation of secret research (Riedel 1986) shows: 22 women had menstruation problems – one third of the tested females. 10 % or 22 female athletes had “problems with medication” – the “pill”. In cumulation that would have been 60 % of the women, who had problems.

12.5 Doping with Children

When an “IM” (volunteers of the state security) in the medical profession was asked about possible side effects, his answer was not only critical, but decimating. The appearance of masculine traits and liver damage had been observed in young girls. The Director of the University Pediatric Clinic, reported of symptoms in one of his young female patients, and the Chief Physician of Pathology at the Oskar Ziehten Hospital discovered liver damage in a group of weight-lifters. Critical voices can be perceived, yet not in public: “uncontrolled high dosages” to minors; for this reason the “medical supervision of steroid prescription” was subjected to limitations. The “presently practiced mode of anabolic steroid implementation in performance sport” contradicted the ethics of “the declared goal of our social order, namely to do everything for the well-being and benefit of mankind.” The same should then be brought to bear for the unnatural burdening of the spine and knee joints (cf. IMS “Philatelist”, Prof. Dr. med. Kurt Franke, BStU ZA MfS ANS AIM 16572/89, Part II, Vol. 4, Report of meeting from July 18th, 1975, pp 105-107, file founded by Teichler, Potsdam).

Last year research in order to give information on victims of the mandatory doping proved, that doping means in Berlin needed dosages, which were 5 times higher than centrally planned by the official medical doctors! These female athletes were juniors at that time, drugged by medical doctors and stately financed coaches, supervised by the state security.

Cover-ups are still regularly reported. But even the following protest by one of the main players in the GDR doping system had no consequences, although – or perhaps precisely because – the president of the “Dynamo Sports Club” became involved: the Minister of State Security himself.

The different symptoms of crisis show clearly how “sport-experiment” athletes in the GDR became increasingly insignificant – as the primary producers of achievement in sports.

Here the doping methods created a specific change. Some of those who were responsible in the GDR, increasingly reduced the sporting “performance” of their stars to the contribution of doping, as the disparaging contemporary expression of “women’s medals” shows. The counter sexual intervention in a woman’s or girl’s personality and hormonal cycle symbolizes the abuse of protégés in the years 1968 to 1990.
A depressing example: in court Dr. med. Gudrun Fröhner, a physician in Leipzig and former chief doctor of the girls in gymnastics, reported to have distributed legal and (possibly) experimental male hormones to 10-12 year old female “gymnasts” – but in her [re-]view as a means of therapy. In the verdict the court agreed with me that these methods could be interpreted as doping.

The “Kaiser-Scheme” was the basis for abusing anabolic drugs: this scheme was used to give hormones to children, who were clearly under the starting line of doping. The “grounded” theory of GDR doping was based on the principle not to give drugs to:

- Boys, as long the connection of the articulation of e.g. the wrist bones is uncompleted, and
- Girls, which have not had their first menstruation.

The ruthlessness of the system is to be seen, when we consider that the official starting age of 18 years for doping was replaced by the construct “biological adult” in the late seventies – any manipulation was possible by that definition.

12.6 New Type of Damage caused by Anabolic drugs

An important medical field is the early abuse of anabolic preparations: the secret East German sport medicine saw new, anabolic induced body damage types in the orthopedic field. The first mentioned were gymnastics and involved both sexes. 1988 a responsible doctor wrote:

In "every female of 'Dynamo' in the national team has damages of the vertebral column. ... The reasons are inner changes of the binding tissue of the articulations. ... The end of loading of the binding tissue has come." (Tb+ IMS „Jürgen Wendt” [Dr. PANSOLD] from 7th of April 1988, II. Bd. 2., p. 224).

Soon the abuse began in female swimmers less than 12 years old. There are even reports that weight-lifters were put on anabolic steroid hormones at the age of 12 or 13 years, which was officially forbidden in the GDR.

The girls in gymnastics should be small from the view of biomechanics. The body height could be stopped by doping. As an effect of anabolics the determination of the longitudinal growth is mentioned in various articles.

Nevertheless, a contemporary witness from Potsdam reported an annual growth in height of 15 cm one year after leaving high performance sport.

12.7 Secret pro-Doping “Science” of the Stately Controlled Mandatory Doping

A first table shows that scientific results about body damages by doping officially existed. In 1986 a researcher added the percentage of side effects in the jump disciplines. Data-basis was a group of 145 drugged athletes.

The table shows the consequences of doping, but only with one anabolic substance! No other compound was co-administered, so that we can assume that even more side effects could appear (see tab. 1, modified from: "Medizinische Nebenwirkungen bei der Anwendung von OT [Oral-turinabol] in unterschiedlichen Dosierungen und Zeiträumen; Männer: n = 85; Frauen: n = 60; cited from Riedel 1986; quoted in: Franke 1995, p 1121).
Tab. 1: Side effects.

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Percentage of side effects:</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased skeletal muscle tonus</td>
<td>65 %</td>
<td>1, 4, 5</td>
</tr>
<tr>
<td>Weight gain</td>
<td>23 %</td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>15 %</td>
<td>1, 3</td>
</tr>
<tr>
<td>Dysmenorrhoe, amenorrhoe</td>
<td>15 %</td>
<td>1, 6, 7</td>
</tr>
<tr>
<td>Problems with other medication</td>
<td>10 %</td>
<td>5, 1</td>
</tr>
<tr>
<td>Acne/ hirsutism</td>
<td>10 %</td>
<td>7, 8</td>
</tr>
<tr>
<td>Changes of libido/ potency/ fertility</td>
<td>8 %</td>
<td>1, 5, 7, 8</td>
</tr>
<tr>
<td>Oedema</td>
<td>2 %</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea/ obstipation</td>
<td>2 %</td>
<td>1, 6</td>
</tr>
<tr>
<td>Functional or morphologic damage of the liver</td>
<td>0-1 %</td>
<td>7, 8, 5</td>
</tr>
</tbody>
</table>

Legend of dosage:
1=Dosage more than 15 mg/day
2=Dosage less than 5 mg/day
3=Short-term treatment (shorter than 14 days)
4=Long-term treatment more than 28 days
5=Medication with “the pill”
6=First medication with anabolics
7=High dosage a year (more than 1000 mg anabolics)
8=Long-term treatment (longer than 5 years)

12.8 Secondary Body Damages by Anabolic Drugs

It is often forgotten that the fast recreation and the high psychological impact on motivation for extreme achievement in the sense of physical load had an unexpected result: extreme exhaustion of the organ system and the body – muscles, bones and connective tissues.

A consequence is that today many former athletes suffer due to doping unnoticeable at the first look. This could be named as “Doping-Syndrom” because it is no illness but a consequence from year-long doping abuse. A result of the case study above? Anyway, it is a problem in dealing with victims today (giving help to the victims).

12.9 Conclusions

Doping of children and younger athletes caused more side effects than in adults: in quality and in quantity. You can also argue about the effectiveness of the system: for medical or political reasons drop-outs did not enter any of the statistics; those who left sports were not looked after.

As you can see today side effects will determine the reality of life for a four-digit number of ex-athletes in GDR sports, and especially the younger athletes. Dangerous “side effects” on body and mind?

Compulsory doping led to other different problems:

- The athletes’ problems to come to terms with their biography;
- Psychological long-term effects as a result of secondary injury like sex-drive dysfunction caused by the consumption of anabolic steroids;
- Injuries which are not experienced (or kept a secret) produce a false judgement on drug use in sports. As a consequence opinions are developed that may be subjectively honest but result in a catastrophe. An example:

"I took UM ["Unterstützende Mittel" = "supportive medications"], but they did no harm because there was medical and sporting control. In the GDR doping wasn't dangerous if you followed the rules."

Here we have to call for the translation of research results from the sports sciences into practice, the noblest goal of social sciences. In my view: there is a need for research by re-analysing (side effects) and aiding (victims).
12.10 References


12.11 Address

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spitzer@rz.uni-potsdam.de
### 12.12 Appendix

**Tab. 2: Side effects.**

**Known side effects, caused only by abuse of anabolic drugs**

<table>
<thead>
<tr>
<th>A</th>
<th>Changes of genotyp – damage on the germ line (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Virilisation of any fetus while abusing anabolic drugs (*)</td>
</tr>
<tr>
<td>2</td>
<td>Mandatory abortion because of pregnancy while training or a half year after competition (*)</td>
</tr>
<tr>
<td>3</td>
<td>Side effects on born children (*)</td>
</tr>
<tr>
<td></td>
<td>- Skin challenge type of allergy</td>
</tr>
<tr>
<td></td>
<td>- Problem with breath of asthma-type</td>
</tr>
<tr>
<td></td>
<td>- Damage of the heart structure/ open heart</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Changes of phenotyp (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Known side effects for both, male and female abusers:</td>
</tr>
<tr>
<td>4.1</td>
<td>Side effects: the skin</td>
</tr>
<tr>
<td></td>
<td>- Seborrhea, so-called “steroid-acne” and “oily skin”,</td>
</tr>
<tr>
<td></td>
<td>- Follikulitis, furunculous</td>
</tr>
<tr>
<td>4.2</td>
<td>Side effects: the liver</td>
</tr>
<tr>
<td></td>
<td>- Abnormal liver functions (e.g. higher serum-transaminase)</td>
</tr>
<tr>
<td></td>
<td>- Cholestase (bile)</td>
</tr>
<tr>
<td></td>
<td>- Histological anomalies of the liver up to peliosis hepatica</td>
</tr>
<tr>
<td></td>
<td>- Androgen-dependent hepatoms (adenoma)</td>
</tr>
<tr>
<td></td>
<td>- Dangerous rips of the same</td>
</tr>
<tr>
<td></td>
<td>- Hepatocellular carcinom (rare)</td>
</tr>
<tr>
<td></td>
<td>- Strong abasement of the HDL-production</td>
</tr>
<tr>
<td>4.3</td>
<td>Different organs of the body:</td>
</tr>
<tr>
<td></td>
<td>- Extreme increase of the tonus in skeleton muscles</td>
</tr>
<tr>
<td></td>
<td>- High blood pressure</td>
</tr>
<tr>
<td></td>
<td>- High risk for brain-hemorrhages</td>
</tr>
<tr>
<td></td>
<td>- Arteriosclerosis, esp. within the heart-wreath-vessels</td>
</tr>
<tr>
<td></td>
<td>- Changes at the structure of the heart muscle</td>
</tr>
<tr>
<td></td>
<td>- High risk from heart attack</td>
</tr>
<tr>
<td></td>
<td>- Increasing water-storage in body cells and connective tissue</td>
</tr>
<tr>
<td>4.4</td>
<td>Disturbances of the psyche and the behaviour</td>
</tr>
<tr>
<td></td>
<td>- Increase of aggression (*)</td>
</tr>
<tr>
<td></td>
<td>- Aggressive psychoses</td>
</tr>
<tr>
<td></td>
<td>- Libido-changes</td>
</tr>
<tr>
<td></td>
<td>- Strong mood-alterations (e.g. “mood swings”, euphoria and/ or depression)</td>
</tr>
<tr>
<td></td>
<td>- Mental disorder, headaches</td>
</tr>
<tr>
<td></td>
<td>- Psychic as well as physical dependence or addiction (*)</td>
</tr>
</tbody>
</table>

| 5. | Specific side effects of male athletes: |
|    | - Testicle-atrophy |
|    | - Disturbances of the seed-education up to the total employment |
|    | - Testicle-aches |
|    | - Growing prostate (hypertrophy) |
|    | - Gynaeecomastia (enlargement of the male breast to female profile) |

| 6. | Specific side effects of female athletes: |
| 6.1 | The skin |
|    | - Dermatology |
|    | - Hirsutism (mustache or beard, male hair growing at the body-trunk) |
|    | - Alopeczie, specifically in male patterns (“Geheimratsecken” loss of hair on the head) |
|    | - Striae distensae (streaky appears in the connective tissue at the body-trunk) |
| 6.2 | Inner organs |
|    | - Abasement of the sexual (steroid) hormones [binding globulin] in the liver, thereby increase of the free testosterone, thereby increasing virilisation |
|    | - Reduction of the breast-gland |
|    | - Lowering of the female voice |
|    | - Strong changes of the menstruation up to long-prolonged type (amenorrhoe) |
|    | - Hypertrophy of the clitoris |
|    | - Atrophy of the uterus |
|    | - Strong changes of the ovary, especially the polycystical ovary-syndrome, ovary-inflammations |
|    | - Decrease of the thyroid gland (thyroxin and thyroxin binding protein) |

13 Health Risks of Nutritional Supplements
Hans Geyer, Maria Henze, Marc Machnik, Ute Mareck-Engelke, Yvonne Schrader, Gerd Sigmund and Wilhelm Schänzer

13.1 Introduction
Athletes are confronted with an enormous number of nutritional supplements. Sports magazines and the internet are overcrowded with advertisements for supplements. Because these preparations are easily available without prescriptions and are sold legally as supplements of the nutrition, athletes often believe, that these products are not connected to health and doping risks. This is a wrong opinion. In this lecture three classes of nutritional supplements are presented, which may lead to health problems and produce positive doping results. These classes are:

- Nutritional supplements with Ma Huang,
- Nutritional supplements with “natural” anabolic androgenic steroids, the so-called prohormones,
- Nutritional supplements, which are contaminated with anabolic androgenic steroids, which are not declared on the label.

13.2 Nutritional Supplements with Ma Huang
Ma Huang is an extract of ephedra plants. It is advertised on the sports nutrition market as fat burner and as generally activating drug. The active compounds of Ma Huang preparations are ephedrine and ephedrine derivatives.

13.2.1 Health risks
Ephedrines have a similar chemical structure as the narcotic drug amphetamine (see fig. 1) and have the same mechanisms of action. The main difference between the ephedrines and amphetamine is an additional hydroxy group in the ephedrine molecule, which makes it more difficult for ephedrines to penetrate through the brain barrier into the central nervous system.

But in high concentrations ephedrines have exactly the same effects as the narcotic drug amphetamine. So it should not be differentiated between weak and hard drugs but between weak and hard use.

Furthermore, there are a lot of health risks connected with the use of “amphetamines” (see tab. 1). Low doses may cause central nervous problems whereas high doses lead to severe cardiovascular problems and paranoid psychosis.
Tab. 1: Health risks.

<table>
<thead>
<tr>
<th>CNS-symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Suppression of orthodoxical and paradoxical sleep</td>
</tr>
<tr>
<td>Loss of body weight by centrally induced anorexia</td>
</tr>
</tbody>
</table>

Cardiovascular toxicity
- Hypertensive crisis and hemorrhages
- Arrhythmias → sudden cardiac death

Disturbance of thermoregulation
- Heat stroke → cardiovascular collaps

Paranoid psychosis
- Auditory hallucinations

The comparison of different pharmaceuticals shows additionally the high potential of dependence and tolerance of the “amphetamines” (see tab. 2).

Tab. 2: Potential of dependence and tolerance of different pharmaceuticals

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Psychic dependence</th>
<th>Physical dependence</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid analgesics</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Ethanol</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Tranquilizers (barbiturates)</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cocain</td>
<td>++</td>
<td>(+)</td>
<td>+++</td>
</tr>
<tr>
<td>Psychostimulants (amphetamines)</td>
<td>++</td>
<td>(+)</td>
<td>+++</td>
</tr>
</tbody>
</table>

13.2.2 Doping risks

The active compounds of Ma Huang supplements are ephedrine and ephedrine derivatives. These substances are on the list of forbidden substances (stimulants) of the International Olympic Committee (IOC) and of the International Sports Federations (IOC 2001). A doping control sample is declared as positive if the urinary concentration of ephedrine and ephedrine derivatives exceed cut off limits defined in the rules. The cut off limit for ephedrine is 10 mikrogramm per milliliter urine (10 µg/ml). In figure 2 results after the application of 2 tablets of a nutritional supplement with Ma Huang are shown. According to the label, this is the recommended dose which should be administered 2-4 hours before exercise. Five hours after the application maximum ephedrine concentrations of 23 µg/ml urine could be detected. These concentrations are far above the cut off limit of 10 µg/ml. As presented in figure 2 the application of these two tablets produced positive doping results for about 9 hours.

Fig. 2: Positive doping results.

In figure 3 are shown the positive cases for ephedrine and ephedrine derivatives detected in the year 1999 in our laboratory.
In 15 of the 29 positive cases, mixtures of ephedrines could be detected in the urine. Such mixtures of ephedrines are indicators for the application of herbal products such as Ma Huang.

### 13.3 Nutritional Supplements with Prohormones

Prohormones are anabolic androgenic steroids, which can be converted in the human body to more active steroids. The most famous prohormones are the prohormones of testosterone and nandrolone (see fig. 4 and 5).

![Prohormones of testosterone](image)

![Prohormones of nandrolone](image)

In many countries these steroids are restricted as medication or are even not permitted, but since 1996 prohormones are sold, especially on the US sports nutrition market, as nutritional supplements. Actually there exist only a few scientific studies about their efficacy but no study about their safety.

#### 13.3.1 Health risks

We have started to investigate the transformation of prohormones to the “active” anabolic androgenic steroids (Machnik et al. 2001). Therefore, we measured the formation of nandrolone after the application of the prohormone norandrostendione. In figure 6 the plasma concentrations of nandrolone after oral administration of 100 mg norandrostendione are presented. The plasma concentrations reach maximum values of 2.1 ng/ml about 1 hour after application of the prohormone. The values obtained after oral norandrostendion application
exceed the maximum concentrations after single injections of 50 mg nandrolone decanoate (mean = 1.2 ng/ml; n=10; grey line in fig. 6 and Belkien et al. 1985) for about 3 hours.

![Graph showing plasma levels of nandrolone after application of norandrostenedione (100 mg orally).]

**Fig. 6: Plasma concentrations.**

If the recommended dose of the prohormone norandrostendione is administered (2-3 x 100 mg per day for several weeks) or if recommendations of several authors in sports magazines are followed (1000 mg per day for several weeks), constant increased plasma levels of nandrolone can be expected, similar to plasma levels after injection of the anabolic steroid nandrolone decanoate. The conclusions of these first results are: high dosage and long-term application of prohormones may lead to the same side effects as the “classic” anabolic steroids. Health risks can be expected especially for women and children.

Additional health risks may result from an insufficient quality control and surveillance of prohormone supplements. Several groups have shown, that many prohormone preparations are falsely labeled (fig. 7).

**Analysis of prohormone-supplements**

Labelling of preparations does not reflect their actual content

- Parasrampuria, M. et al. 1998: DHEA supplements contain 0-150 % of declared content.
- Ayotte, C. et al. 1999: androstendione- and androstendiol-supplements contain additionally testosterone, androstadiol and epitestosterone

**Fig. 7: Nutritional supplements.**

Our own investigations confirmed these results. In figure 8 an example of a falsely labeled prohormone supplement is presented.

**Falsely labeled prohormone supplement**

**Declared content:**
- 19-nor-5-androstenediol

**Actual content:**
- 5-androstenediol

**Fig. 8: Labelling mistakes.**
So it cannot be estimated which substance and which concentration can be expected in prohormone supplements.

13.3.2 Doping risks

The prohormones of testosterone and nandrolone are on the list of forbidden substances (anabolic agents) of the International Olympic Committee (IOC) and of the International Sports Federations (IOC 2001). They are forbidden in competition and out-of-competition. The misuse of prohormones of testosterone can be detected in doping control by the increase of the ratio testosterone/epitestosterone or the change of other parameters of the steroid profile or by changed carbonisotope ratios of testosterone and its metabolites. The misuse of prohormones of nandrolone can be detected by the common urinary metabolite norandrosterone (see fig. 9).

![Fig. 9: Metabolism of the prohormones of 19-nortestosterone (nandrolone).](image)

In figure 10 the norandrosterone concentration after a single oral application of one capsule (100 mg) of a norandrostenedione supplement is shown. The norandrosterone concentrations exceed the cut of limit of the IOC (2 ng/ml for males) for about 9 days. If the recommended doses (several capsules per day for a long time period) are taken, much longer time periods for positive results can be expected.

![Fig. 10: Concentration of norandrosterone [ng/ml] after oral application of 100 mg norandrostenedione.](image)

13.4 Nutritional Supplements contaminated with Prohormones

In May 1999 we started to analyse non-hormonal nutritional supplements such as vitamins, minerals, creatine, carnitine etc. for prohormones in our laboratory. Up to February 2001 we analysed 153 supplements. The following results were obtained (Geyer et al. 2000, 2001): 18 different supplements from 12 different companies contained prohormones, not declared on the label. 15 of the 18 supplements contained prohormones of nandrolone. The positive supplements were bought in USA, UK, Sweden, Norway, Belgium, Austria and Israel. The not-declared prohormones occured in different matrices as tablets, capsules, powders, drinking ampouls and oily solutions (see tab. 3).
Tab. 3: Analysis results.

Contamination of nutritional supplements

- Creatine
- Carnitine
- Vitamines + minerals
- Tribulus terrestris
- Ribose
- BCAA
- OKG
- Zinc
- Pyruvate
- Chrysin
- Guarana
- CLA and other oils
- Herbal extracts
- Glutamine

In table 3 the supplements in which the prohormones were found are listed. Most positive supplements contained more than one prohormone.

Figure 11 shows a GC/MS chromatogram of a creatine product in which 7 different prohormones and even testosterone were detected.

![GC/MS Chromatogram](image)

**Fig. 11: Not declared prohormones in a creatine product.**

The concentrations of the prohormones in the capsules or tablets are presented in figure 12.

![Concentrations of prohormones](image)

**Fig. 12: Contamination frequencies.**

About 80% of the positive-tested supplements contained prohormones in concentrations lower than 100 µg/capsule or tablet. That means, that most concentrations are more than a factor of 250 lower than the lowest concentrated prohormone preparation on the supplement market (25 mg). We think that the prohormones are not intentional admixtures to supplements but so-called cross-contaminations. Indicators for cross-contaminations are low concentrations of the contaminants and a large variation of the concentrations. Both conditions are fulfilled.

Figure 13 shows the strong variation of the concentrations of prohormones from capsule to capsule and charge to charge in a tribulus terrestris product. The reason for the cross-contaminations is an insufficient cleaning of machines and vessels involved in the manufacturing and transport of prohormones. If the same machines and vessels are used afterwards in the processing and transport of other supplements as vitamines, minerals etc. cross-contaminations with prohormones may occur, especially in the first products of a charge.
Cross-contamination
low concentrations
variation of concentrations from capsule to capsule

<table>
<thead>
<tr>
<th>TRIBULUS TERRESTRIS</th>
<th>Charge 1</th>
<th>Charge 2</th>
<th>Charge 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kap1</td>
<td>0.3</td>
<td>0.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Kap2</td>
<td>0.4</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Kap3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

4-androstendione (µg/capsule)
Kap1 Kap2 Kap3 Kap1 Kap2 Kap3 Kap1 Kap2 Kap3
1,3 0,3 76,3 0,6 2,2 0,0 1,2 1,4 0,8
5-androstendiol (µg/capsule)
Kap1 Kap2 Kap3 Kap1 Kap2 Kap3 Kap1 Kap2 Kap3
4,1 0,1 0,1 0,0 0,0 0,0 0,0 0,0 0,0
16,6 30,1 5,6
4-androstendiol (µg/capsule)
Kap1 Kap2 Kap3 Kap1 Kap2 Kap3 Kap1 Kap2 Kap3
0,7 1,5 3,3 1,4 0,8 0,6 1,4 3,8 0,6
5-androstendiol (µg/capsule)
Kap1 Kap2 Kap3 Kap1 Kap2 Kap3 Kap1 Kap2 Kap3
0,04 0,04 0,04 0,00 0,00 0,00 0,00 0,02 0,00
4-norandrostendione (µg/capsule)
Kap1 Kap2 Kap3 Kap1 Kap2 Kap3 Kap1 Kap2 Kap3
0,04 0,04 0,04 0,1 0,1 0,1 0,1 0,1 0,1
4-norandrostendiol (µg/capsule)
Kap1 Kap2 Kap3 Kap1 Kap2 Kap3 Kap1 Kap2 Kap3
0,74 1,36 1,36 1,36 1,36 1,36 1,36 1,36 1,36

Fig. 13: Variation of prohormone concentrations in capsules.

13.4.1 Health risks

Because nutritional supplements are taken for a long-time period without any restriction regarding dosage and because the concentrations of the prohormones in the contaminated supplements can be in the milligram-region (see fig. 12), side effects as after the application of “classic” anabolic steroids cannot be excluded especially for children and women.

13.4.2 Doping risks

Doping risks result especially from nutritional supplements contaminated with prohormones of nandrolone. As mentioned before, prohormones of nandrolone lead to a common urinary metabolite norandrosterone (see fig. 9). Concentrations of norandrosterone above the cut off limits of 2 ng/ml for males and 5 ng/ml for females lead to positive doping results.

We performed excretion studies with nutritional supplements contaminated with different amounts of norandrosterone. In figure 14 the resulting concentrations of norandrosterone are shown. After application of supplements contaminated with 5.6 and 3.7 µg norandrosterone, positive results (for males) for about 4 hours could be obtained.

Fig. 14: Excretion study results.

In consideration of much higher concentrations of the contaminants (see fig. 12) and a long-term and high dosed application of supplements, positive results with much higher concentrations of norandrosterone and longer time periods of positive results can be expected (Geyer et al. 2000).

To minimize the risks of an unknowingly positive doping result by the application of a contaminated nutritional supplement, athletes should only take supplements from companies, which perform a quality control for prohormones or/and which can confirm, that they have no contact (in manufacturing and transport) with prohormones.
13.5 Conclusions

Nutritional supplements with Ma Huang and prohormones are connected with health and doping risks. Additional health and doping risks result from an insufficient surveillance of the manufacturing and production of prohormone supplements (contaminated supplements, falsely labeled supplements).

13.6 References


13.7 Address

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14  **Nutritional Supplements and Doping**

Frans Delbeke

14.1  **Introduction**

The use of nutritional supplements in sports but also outside sports is widespread. Even for professional athletes the temptation of experimenting with these supplements is high. A strong indication of this trend comes from the increased sales of herbal medicines in the US and the easy availability of so-called natural products promoted on the internet.

The story started some years ago when suddenly the Paris doping laboratory detected small amounts of nandrolone metabolites in the urine of professional athletes including an Olympic medallist in judo and several French soccer players. More recently soccer players in Italy were tested positive for nandrolone as well.

The number of nandrolone cases steadily increased in recent years and famous athletes including Linford Christie and Merlene Ottey were confronted with positive nandrolone tests.

14.2  **The History**

Contamination of food supplements and herbal medicines however is not new. Already in the 80’s a Belgian female marathon athlete was very surprised to hear that she was tested positive for the stimulant phentermine after a major athletic meeting in Portugal. She claimed that she never had used doping agents. The only medicine she took were natural products for weight loss, bought in a reform store.

When we analysed those herbal mixtures we found – to our surprise – that the plant ingredients were not responsible for the weight loss effect but that these preparations were deliberately contaminated with the anorexic agents phentermine and fenfluramine.

To some of the mixtures phentermine was added, other batches contained fenfluramine and phentermine, both substances with stimulant properties and appearing on the doping list of forbidden substances.

Afterwards, several cyclists tested positive in our lab for ephedrine. They had no cold, they didn’t use cough syrups containing ephedrine, only the nutritional supplement “Diet Full” from “Twin Lab”, an “innocent” thermogenic herbal preparation. On the back side of the bottle however the tablets appear to contain alkaloids from Ma Huang and guarana, in other words the forbidden substances ephedrine and caffeine (see fig. 1).

![Nutritional supplement](image)

**Fig. 1: Nutritional supplement.**

Ma Huang is a Chinese medicine. Several athletes tested positive for ephedrine after the intake of this rather dangerous herbal preparation. Indeed, in recent years the American Food and Drug Administration has received an increasing number of reports of adverse reactions associated with the use of herbal Ma Huang. Among the reported reactions are hypertension, palpitation, stroke and memory loss. The American Herb Research Foundation has recently taken the position that the adverse effects of Ma Huang are dose-dependent and that it is safe when “used in reasonable amounts by normal consumers”. The question remains however whether some athletes are normal consumers using reasonable amounts.

Also the general non-athletic population is using this kind of product. The sales of dietary supplements which include nutritional and herbal preparations in the US have surged to more than 14 billion in 1999 from 8.3 billion in 1994.
14.3 Guarana

Another source of inadvert doping is the use of guarana. In the last years the use of energetic drinks and ground guarana seeds by mostly young people in fitness gyms and night clubs aiming to reduce fatigue and increase the state of alertness has dramatically increased.

In Europe guarana drinks, extracts and capsules are sold not only in fitness centres but also in bike shops. The use of these products can lead to caffeine positive doping tests. Surprisingly, it seems that some guarana preparations contain deliberately added caffeine itself.

14.4 Supplements and Anabolic Steroids

But let’s focus on food supplements and anabolic steroids. Actually there is some confusion or misunderstanding about food supplements. On the one hand we have substances like dehydroepiandrosterone (DHEA), norandrostenedione and norandrostenediol. These so-called dietary supplements are real anabolic steroids freely available in the US and through internet and do not have to pass the stringent quality controls imposed on approved medications.

Their claimed actions, efficiency or potency are not thoroughly investigated by controlled clinical studies and remain for the most part anecdotal. The adverse effects are not fully known. These hormonal, so-called dietary supplements available for self administration are not evaluated by the USA Food and Drug Administration (FDA) for their safety and efficacy.

Their production and manufacturing do not have to be in compliance with the regulations of the FDA neither do they have to meet the standards of quality. For instance, a group of American scientists reported the results of the analysis they made on sixteen different DHEA preparations in different dosages. They found that the actual content of this steroid ranged from 0 % to 150 % of the dosage indicated on the labels.

Another example: in Sweden some supplements supposed to contain androstenediol alone or in combination with androstenedione that were seized at the customs were shown to contain testosterone, a regulated substance.

Years ago Irish smugglers carrying 3 sportbags full of anabolic steroids were arrested by the Belgian customs. When we analysed the perfectly imitated packages most of the products were fake with stanozolol tablets containing glucose and decadurabolin vials containing testosterone instead of the nandrolone ester. Each person with a basic knowledge of chemistry knows that the synthesis of testosterone is much easier and more profitable than the manufacturing of other anabolic steroids.

Another concern is related to the so-called contaminated supplements. Products including creatine, amino acids, branched amino acids and guarana which are, at least in my opinion, deliberately contaminated with anabolic steroids including nandrolone or nandrolone precursors.

In order to fully understand the nandrolone positive cases in recent years I would like to present the different ways of testing positive for nandrolone.

First of all, nandrolone injections, mostly nandrolone esters which are slowly released from the injection site resulting in a detection time in the laboratory of approximately 6 months. However, nandrolone also exists in tablets for oral administration. Detection time in the lab is 3-4 days. The same applies for the nandrolone precursors, substances including norandrostenediol and norandrostenedione which are converted in the body to nandrolone. Detection time is also 3-4 days, depending on the dosage.

14.5 Nutritional Supplement Products from Fitness Studios

In the framework of a project of the European Community with the Ministry of Interior of Low Saxony we started analysing food supplements that were bought in fitness studios in Germany, Portugal, Switzerland and in the Italian province of Alto Adige or South Tirol. Most of the products we received from several fitness studios were proteins, amino acid mixtures or so-called massive weight gainers.

We were not able to detect anabolic steroids in samples sold in any one of the German fitness studios. The samples we received from Germany contained proteins with different flavours including citrus, vanilla, banana, cherry and chocolate, but nandrolone precursors and other anabolic steroids were not found.

The samples bought in Portuguese studios were of American origin with very promising names including massive weight gainers or anabolic fuel. However neither nandrolone precursors nor other anabolic steroids could be detected.
From Switzerland we received 12 supplements (including Xtreme Creatine, Aminovit, Super Amino 2000, Max Gain, Gainer 3600 and others). In one of them, a branched chain amino acid preparation, we found the nandrolone precursor 19-norandrostenedione.

At present other samples from South Tirol, Flanders and Germany remain to be analysed.

### 14.6 Contaminated Food Supplements

However I would like to finish this presentation by showing you some contaminated food supplements detected in our laboratory during the last year.

For instance, a branched amino acid hydroxymethylbutyrate contaminated with 19-norandrostenedione, iron tablets contaminated with 19-norandrostenedione or a Guarana supplement found to contain androstenedione, norandrostenedione and testosterone. Finally a food supplement containing guarana, carnitine, choline, cayenne powder, vitamin B 6 and other substances described as “plus much more”. This “much more” was androstenedione and norandrostenedione with a concentration of approximately 6.3 mg/g for the nandrolone precursor (see tab. 1).

<table>
<thead>
<tr>
<th>Tab. 1: Food supplement.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anabolic steroid concentrations:</strong></td>
</tr>
<tr>
<td>4-androstene-3,17-dione</td>
</tr>
<tr>
<td>19-nor-4-androstene-3,17-dione</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>4-androstene-3,17-dione</td>
</tr>
<tr>
<td>19-nor-4-androstene-3,17-dione</td>
</tr>
</tbody>
</table>

Recommended intake: 7 capsules

### 14.7 Excretion Study

We performed an excretion study with only one capsule (the manufacturer’s recommendend dose were 7 capsules) in 5 subjects. During this study, norandrosterone, the major norandrostenedione metabolite, was mainly excreted in the first 24 hrs after oral intake. According to the IOC treshold level of 2 ng/ml in urine of males, positive findings were noticed within 48 hrs and in one case even until 144 hrs after the intake (see fig. 2 and 3).

![Urinary excretion of norandrosterone](image1.png)

![Urinary excretion of norandrosterone (72-192 hrs)](image2.png)

*Fig. 2 and 3: Excretion study results.*
Athletes and also owners or trainers of fitness studios should consider that most nutritional supplements do not pass appropriate quality tests as for registered drugs and that there is no guarantee that these supplements contain no banned substances.

Another consideration is the daily intake of contaminated food supplements. In the last case the manufacturer recommended seven capsules on a daily basis. One can imagine what the health effects would be after the intake of these supplements during an extended period of time.

In conclusion, in order to protect the health of athletes and also of people exercising in fitness studios, measures should be taken to stop the production and import of these unlicensed nutritional supplements.

14.8 Address

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15 Androgen related Prohormones as Nutritional Supplements – are their Use worth the Risk
Craig E. Broeder

15.1 Introduction
Several years ago, it was discovered that Mark McGwire was taking the supplement androstenedione during his historic year in baseball. At the time, our research group was developing an anti-aging study using androstenedione. As you are all aware of by now, androstenedione or “Andro” as it is commonly called is very aggressively marketed as a testosterone and performance enhancing dietary supplement. This is the direct result of the passing of the 1994 Dietary Supplement and Health Education Act (DSHEA) passed by the United States Congress. As you have already heard, this act has led to a number of supplements that are being marketed in the United States and throughout the world that place athletes at potential serious health risks and sanctions from international athletic organisations world wide.

Originally, the food supplement act was designed to allow people the use of common vitamin supplements such as vitamin C. However, through several loop-holes in the law, any substance that is natural to the body even if it is not commonly found in food can be sold under this act. This is unfortunate because it has led to a number of companies simply attempting to take advantage of these loop-holes to their own financial rewards regardless of the outcomes. In other words, consumers in America and the world, because of the internet, are being provided untested, unproven, and potentially lethal products every day (see tab. 1).

I will briefly provide several introductory comments about the marketing and seductive sale practices of Andro related supplements. I will also provide a brief overview of the two most popular forms of Andro, androstenediol and androstenedione marketed today. And finally, I will provide you with data from our group and others regarding what is currently known about the physiological and biochemical effects of acute and chronic Andro use.

Andro supplements are promoted to improve strength and athletic performance, reduce body fat, increase muscle mass, prevent fatigue, make a person feel 20 years younger, and enhance a person’s sexual performance. The promotion of Andro is done through many seductive advertisements (see tab. 2).

For example, as you can see in this next figure that was taken from a mailing advertisement, Andro manufacturers take distinct advantage of the fact that Mark McGwire, a famous baseball player was using Andro.
In addition, the advertisers also appeal to a man’s sexual desires with the use of a pretty woman scantily dressed in a two piece bath suit. They also supposedly support their claim with an article published by a medical expert. Unfortunately, in this case, the medical expert is not qualified to speak on Andro supplementation since this is not his formal research area of expertise.

You can observe that once again the advertisers link a man’s sexual ability to testosterone and how Andro can be the answer (see fig. 2).

And, just in case the sex appeal, the Mark McGwire connection, or the medical expert do not convince you to try Andro, they scare you to death by stating “your penis shrinks 19.8 % as you get older due to deficiency of testosterone” (see fig. 3). However, as you will see, in vivo data from our lab does not support these findings.

Currently, Andro supplements are commonly termed prohormones. They are designated as prohormones because they are precursor substances to highly functional hormones such as testosterone as one can see in the biochemical pathway shown in the current figure (see fig. 4). During the synthesis of testosterone, there are two primary pathways, the delta-4 and the delta-5 pathway.

Fig. 1: Elite baseball player.

Fig. 2: Sales promotion.

Fig. 3: Sales promotion.

Fig. 4: Biochemical pathway.
In vitro studies indicate that the delta-5 pathway through androstenediol converts to testosterone more easily than the delta-4 androstenedione pathway. However, as you will see, in vivo data from our lab do not support these findings. One of the first studies to investigate the physiological and biochemical effects of Andro supplementation was by Doug King’s group at Iowa State University (1999, see tab. 3).

Tab. 3: Scientific study.

**Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men:**

Clinical investigation: a randomized controlled trial

King et al.:

Results summary serum free & total testosterone not effected by short-term (360 mins post 300 mg of Andro) and long-term use (8 weeks).

Serum estradiol and estrone were significantly elevated with chronic Andro use.

Andro had no enhancing effects on strength or body composition.

A significant decline in HDL-c was observed.

JAMA 281 (21): 1999

They found no significant chronic effects on free and total testosterone levels, body composition, or strength after 8 weeks use of 300 mg/day. They did find that there were however significant elevations in serum estradiol and estrone levels and a significant reduction in HDL-c. This data suggested that several common claims regarding Andro use might increase the potential risks of heart disease, stroke, prostate, and pancreatic cancer without any potential performance enhancing benefits. To date all studies have verified a majority of data presented in the study of King and colleagues (1999).

In one of the first studies by our group, we determined the acute effects of 200 mg/day of either androstenedione versus androstenediol supplementation in young men (Earnest et al. 2000, see fig. 5).

The results of this study indicate that androstenedione produced a significant increase in the area under the curve in total testosterone for 90 minutes post oral supplementation. These results are similar to the acute responses Doug King’s group observed in their study. However, it is important to realize that simply because we can acutely increase a person’s testosterone level, it does not automatically imply that chronic testosterone level will remain elevated nor does it imply any potential functional improvements in say strength or sexual performance.

Interestingly, in a study by Rasmussen and colleagues (2000), using tracer technology with phenylalanine and a three compartment model of leg muscle amino acid kinetics, they showed that Andro supplementation has more potential catabolic versus anabolic activity (see fig. 6).
Androstenedione's effect on muscle protein synthesis using tracer technology

Three-compartment model of leg muscle amino acid kinetics

Fig. 6: Scientific results.

As you can see in the next table, the greatest tracer effect of Andro supplementation occurred for protein breakdown (see tab. 4). As a result when Rasmussen and colleagues (2000) looked at the protein catabolic to anabolic ratio, they found that this ratio increased. This result is not surprising because in rats, high estrogen concentrations have been shown to lead to type 2 muscle fiber breakdown. These findings together may help to indicate why there were no significant enhancements in strength or body composition in the King and colleagues study.

Tab. 4: Androstenedione's effect on muscle protein synthesis using tracer technology.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dione</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Protein breakdown</td>
<td>69 ± 10</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>44 ± 9</td>
<td>59 ± 12</td>
</tr>
</tbody>
</table>

Data expressed as nanomoles per min/100 ml leg vol (mean ± SEM)
*p ≤ 0.07 for time effect within dione group.

15.2 The Andro Project

In our most recent study just published in the Archives of Internal Medicine, we attempted to look at a variety of claims by developing a very detailed study. Today I will present to you the main findings report in our Archi's article and the newest data we have just completed on the potential hormonal risks for prostate and pancreatic cancer development (see tab. 5).

Tab. 5: Potential hormonal risks.

The “Andro Project”: the physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high intensity resistance training program

Clinical investigation

Broeder et al.:

Purpose: To elucidate the effects oral androstenediol or androstenedione supplementation had on muscle strength, body composition, hormonal profiles, kidney and liver function, blood chemistry, pulmonary function, echo-cardiogram measured cardiac function, bone density and bone turn-over, dietary intake, psychological profiles of mood and sexual behaviour.

Arch Int Med 160 (20): 2000

As you can see from the next figure, we performed a series of procedures including hormonal profiles, strength tests, and body composition including bone turnover and density assessment. In addition, after pretesting, subject's consumed 200 mg/day of placebo, androstenedione, or androstenediol while each subject participated in an intense resistance-training program. I would like to point out that each person's work was conducted by a
personal trainer in which the exact number of repetitions, sets, exercise start and finish times were recorded. As a result, we were able to look at not only the strength from a 1-repetition max perspective but also the total amount of weight lifted, total amount of weight lifted per workout, and total amount of weight lifted per second (see fig. 7):

![Testing & study design](image)

- **Testing & study design**
  - Pre-test
    - Hormonal profiles
  - 12 Weeks resistance training program and prohormone supplementation
    - 3x/wk Varying intensity 65%, 80%, 90%, 95%
    - Personal trainer assisted subjects each session
  - Post-test
    - Serum hormone profile data at 0, 4, 8, & 12 weeks
    - Full body workout each training session: 2-day split program, 1 day recovery following each session

Fig. 7: Scientific study structure.

Initially 71 subjects were recruited for this study but after drop-outs, the final data pool included 50 men between the age of 35 and 65 years as can be seen in this next table (see tab. 6).

**Tab. 6: Subject population items.**

<table>
<thead>
<tr>
<th>Pre-screening included 71 volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>o 5 subjects were not allowed to start due to positive ST-segment depression or high blood pressure</td>
</tr>
<tr>
<td>o 1 subject omitted due to mitral valve prolapse</td>
</tr>
<tr>
<td>o 2 subjects dropped out due to lack of compliance</td>
</tr>
<tr>
<td>o 12 more dropped out due to personal conflicts</td>
</tr>
<tr>
<td>o 1 subject was removed due to exceedingly high testosterone levels</td>
</tr>
<tr>
<td>Final Subject Pool: placebo = 18; diol = 17; and dione = 15</td>
</tr>
</tbody>
</table>

Regarding the subjects’ characteristic table, there were no significant differences between the groups at the start of the study in age, weight, BMI, percent body fat, and aerobic capacity (see tab. 7). As you will see in later tables, there were also no differences between the groups with regard to their initial hormonal profiles or strength measures.

**Tab. 7: Subject characteristics (mean ± SD).**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Diol</th>
<th>Dione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>47.0 ± 8.4</td>
<td>47.0 ± 8.7</td>
<td>43.1 ± 6.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.9 ± 14.8</td>
<td>89.6 ± 13.6</td>
<td>88.0 ± 16.5</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 3.5</td>
<td>29.3 ± 4.1</td>
<td>27.9 ± 4.1</td>
</tr>
<tr>
<td>% Body fat</td>
<td>20.4 ± 8.0</td>
<td>19.9 ± 4.2</td>
<td>18.6 ± 6.8</td>
</tr>
<tr>
<td>Fat-free mass</td>
<td>69.2 ± 7.8</td>
<td>71.5 ± 9.4</td>
<td>71.0 ± 3.2</td>
</tr>
<tr>
<td>VO₂max</td>
<td>39.0 ± 6.5</td>
<td>38.1 ± 6.8</td>
<td>39.6 ± 5.8</td>
</tr>
</tbody>
</table>

As you can see in the initial hormonal profile tables, each groups’ values were well within the normal expected clinical serum blood values for each of the hormones measured. However, after the 12 weeks of either androstenediol or androstenedione supplementation, several highly significant changes occurred (see tab. 8 and 9).
We can see that after 12 weeks of high intensity resistance training, none of the hormonal values in the placebo were chronically altered (see tab. 9). However, several significant changes were observed in both supplemental groups. First, it is interesting to note, that as in Doug King’s study total testosterone, free testosterone as well as SHBG were not significantly altered at the end of 12 weeks of resistance training and supplement use. In addition, as previously shown, the main effect of androstenedione and androstenediol use, is a dramatic increase in estrogen related compounds. Also, there appears to be a distinct difference in the hormonal responses of the dione and diol supplements in that serum androstenedione was increased most by the dione supplementation while DHEAS significantly increased the most with the diol use.

It is important to remember that hormonal changes are dynamic and that simply looking at hormonal profiles for just two distinct time periods may not provide an adequate picture. For example, one can see in figure 8 for total testosterone changes, that significant increases were observed in months 1 and 2 in the androstenedione group only.

However, by the post testing period, the dione group's total testosterone levels returned to baseline. Similar changes were observed in the dione group's free testosterone levels.
In contrast, one can see that the estradiol concentrations increased quickly and remained elevated throughout the study while the diol supplementation resulted in elevated estradiol concentrations by the 3rd month (see fig. 9).

![Graph showing estradiol changes](image)

*Fig. 9: Estradiol changes ($\S = $ dione sign. greater than placebo, $p < 0.05$; $\# = $ diol sign. greater than placebo, $p < 0.05$; $\dagger = $ dione sign. greater than diol, $p < 0.05$).*

As a result, when all measurements periods are averaged, estradiol concentrations were significantly elevated in both the diol and dione group for the entire study period while testosterone levels only neared significance in the dione group (see fig. 10).

![Graph showing testosterone and estradiol levels](image)

*Fig. 10: Cumulative effect of Andro on estradiol & testosterone level ($\S = $ dione group to placebo, $p = 0.08$).*

What is very interesting to note is what effect androstenedione supplementation had on serum luteinizing hormone levels (LH). One can see that after just 1 month of use, LH serum levels were down-regulated 33% and remained 18% lower than baseline values (see fig. 11).

![Graph showing percent change in testosterone and LH](image)

*Fig. 11: Effects of androstendione on serum total testosterone and LH levels (comparing percent change from baseline for all measurement periods; $p = 0.09$).*
As a result, serum total testosterone levels returned to baseline by the end of the 12th week of dione use. This data suggests that even though androstenedione is a weak androgen, it still has the potential to down-regulate a person’s endogenous testosterone production by lower serum LH levels.

In regard to performance, one can see from the strength training workout results, that our subjects were involved in an intense weight training program lifting between 316.4 to 359.7 kgs of weight between weeks 2 and 11 of the study (see tab. 10). You can also see that while there were no significant differences in weight lifted per minute, there was a trend of the dione group to lift more weight per unit of time.

<table>
<thead>
<tr>
<th>Training period</th>
<th>Placebo (n=18)</th>
<th>Diol (n=17)</th>
<th>Dione (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sums for weeks 2 to 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total weight Lifted (kg)</td>
<td>316.5 ± 79.2</td>
<td>359.7 ± 93.6</td>
<td>352.8 ± 67.2</td>
</tr>
<tr>
<td>Weight lifted (kg/min)</td>
<td>141.4 ± 32.8</td>
<td>159.2 ± 42.5</td>
<td>162.4 ± 29.9</td>
</tr>
</tbody>
</table>

This data suggests that the dione group should have the greatest potential for strength adaptation gains. But as you will see, this was definitely not the case (see tab. 11).

All groups showed a significant improve in strength but there were no significant differences between any of the groups. Thus, Andro supplementation has no effect what so ever on enhancing the adaptations to training in our study as might be expected from the dione group’s trend to lift more weight per unit time.

| Tab. 11: Effects of Andro on strength (significance pre to post: p ≤ 0.01). |
|-----------------|-----------------|-----------------|-----------------|
| Pre             | Post            | Post            | Post            |
|                 | Placebo         | Diol            | Dione           |
| 1-RM Sum (kg)   | 276.4           | 298.9           | 302.0           |
| 1-RM Sum/FFM (kg) | 3.97           | 4.11           | 4.23           |
| 1-RM Sum/SMM (kg) | 6.9           | 7.2           | 7.2           |
| Post            |                 |                 |                 |
|                 | Placebo         | Diol            | Dione           |
| 1-RM Sum (kg)   | 334.1*          | 347.2*          | 356.7*          |
| 1-RM Sum/FFM (kg) | 4.74*          | 4.77*          | 4.96*          |
| 1-RM Sum/SMM (kg) | 8.2*           | 8.2*           | 8.7*           |

In addition, even when we looked at the strength adaptations in regard to initial strength, there once again appears that Andro use exerted no distinct advantage for strength training adaptations compared to placebo conditions with weight training (see fig. 12).

![Fig. 12: Strength effects continued (* = sig. strength improvement from pretreatment period; p < 0.05).](image)

However, as King and colleagues (1999) previously showed, there was a very significant increased cardiac related lipid risk profile using the (LDL/HDL)/(Apo a/Apo b) ratio in our study (see fig. 13). In fact, as one can see, the high intensity weight training program led to a 12.3 % reduce lipid risk profile in the placebo group while the diol and dione group showed a 5.2 % and 10.5 % increase, respectively. Thus, the positive benefits normally exerted as a result of a quality strength training program, were completely reversed after Andro supplementation.
Fig. 13: Cardiac lipid profile risks (based on [LDL/HDL]/[Apo a/Apo b]).

Finally, we believe it is important to highlight any potential evidence of risks associated with the use of prohormone supplementation. Using the methods of Barrett-Conner and colleagues (1990) you can see that with weight training alone there was a 5.8 % reduction in relative risk (RR) for prostate cancer which accounts for age, body weight, and BMI differences (see tab. 12). In dramatic contrast, the diol group showed a 43 % potential increase while the dione group showed a 106 % potential increase.

Tab. 12: Age-adjusted relative risks (RR) of prostate cancer development based on androstenedione concentrations.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Diol</th>
<th>Dione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-test</td>
<td>2.60</td>
<td>4.25</td>
<td>5.69</td>
</tr>
<tr>
<td>Post-test</td>
<td>2.45</td>
<td>4.25 #,†</td>
<td>5.69 #,§</td>
</tr>
<tr>
<td>% change from baseline</td>
<td>(-5.8 %)</td>
<td>(+43 %)</td>
<td>(+106 %)</td>
</tr>
</tbody>
</table>

RR calculations based on androstenedione concentrations according to Barrett-Conner et al. 1990, Cancer Research. Dione concentrations of 0-2.0 nmol/l = a RR of 1.0.

# - significantly > pretesting (p = 0.03); †- significantly > placebo (p = 0.01); § - significantly > diol (p = 0.01). Broeder et al. JAMA 2001 (in review)

In addition, when one looks at the serum dione concentrations of total testosterone (TTES) levels, resistance training alone reduced that groups risk by 18.6 % using the model developed by Fernandez-del-Castillo and colleagues (1990). As observed in the previous table the diol group showed a mild increase in pancreatic cancer risk of 8.9 % while the dione group showed a stunning 172 % increase in potential risk of pancreatic cancers (see tab. 13).

Tab. 13: Increase in dione: TTES have been linked to pancreatic cancers.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Diol</th>
<th>Dione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-test ratio</td>
<td>0.43 ± 0.18</td>
<td>0.56 ± 0.61</td>
<td>0.39 ± 0.15</td>
</tr>
<tr>
<td>Post-test ratio</td>
<td>0.35 ± 0.16</td>
<td>0.64 ± 0.23</td>
<td>1.06 ± 0.65</td>
</tr>
<tr>
<td>Adjusted post-test ratio</td>
<td>0.35 ± 0.18</td>
<td>0.64 ± 0.23 #</td>
<td>1.06 ± 0.40 †</td>
</tr>
<tr>
<td>% change from baseline</td>
<td>(-18.6 %)</td>
<td>(+8.9 %)</td>
<td>(+172 %)</td>
</tr>
</tbody>
</table>


# - significantly > pretesting (p = 0.03); †- significantly > placebo and diol (p = 0.01).

Broeder et al., JAMA 2001 (in review)

In summary, based on our work and that of King and colleagues, Andro supplementation has no effect on body composition, strength, or permanent enhancement of total or free testosterone when taken in dosages recommended by manufacturers (see tab. 14). It does not appear to enhance mood states or sexual performance. But there is strong evidence that a person’s cardiovascular disease and cancer risk profiles significantly move in a negative direction.
Tab. 14: Other Andro investigated items.

- No significant effect on body composition with regard to muscle mass gains or fat loss.
- No significant effect on mood states such as vigor, depression, or anger.
- No significant improvement in perceived sexual performance of any kind.
- No indication that prostate, liver, or kidney function are negatively altered in low dose use.
- Preliminary data analysis indicates that bone-turn-over was improved with more osteoblastic activity than osteoclastic activity occurring.

And finally, more recent studies (see tab. 15) appear to confirm our work and the original work of King and colleagues (1999). Thus, it is my opinion, that unless Andro related supplements are taken in very high supra-physiological dosages, the ergogenic benefits suggested by manufacturers are not likely to occur.

Tab. 15: Other significant findings.

- Androstenedione has been shown to produce positive urine tests for nandrolone (Catlin et al. 2000, Uralets and Gillette 2000). In addition, the study of Catlin and colleagues highlighted the potential for impurities and/or inaccurate labeling of Andro type supplements.
- In older men (> 50 yrs of age) significant increases in free-testosterone level have been observed up to 8 weeks of use for either 300 mg/day of androstenedione or androstenediol (Brown et al. 2000 and Brown et al. 2001 (in press)).
- When dosages are 200 mg or greater per day, significant declines in HDL levels occur (King et al. 1999, Broeder et al. 2000, and Brown et al. 2000, Brown et al. 2001 (in press)).
- The use of natural aromatization blockers such as chrysin and indole-3-carbinol do not block the excess conversion of androstenedione or androstenediol to estrogen (Brown et al. 2001).

However, it is very important to understand, even if supra-physiological dosages do exert some ergogenic benefits, the potential for cardiovascular disease or cancer development appear extremely likely, giving the fact that mild to moderate dosages have been shown to dramatically increase a person's risk of developing these diseases. And thus, it is more likely that instead of getting the girl as a result of using Andro supplements, you are more likely to become the girl as shown in our last figure (see fig. 13).

Fig. 13: Title of the picture: “Less than 0.5% of performance enhancing chemicals have any noticeable side effects”.

15.3 References


15.4 Address

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16  Doping Abuse in Recreational Sports  
Vassilis Mougios

16.1 Introduction
Doping has been traditionally linked to competitive sport. Use of banned substances by top athletes not only monopolizes the attention of the media and, hence, the public, but is the focus of the vast majority of the relevant scientific literature as well. Unfortunately, doping is not confined to athletes competing for a medal, but is also spread throughout gymnasia, health clubs and other recreational sporting facilities and activities. The aim of this presentation is to shed some light on this part of the problem of doping.

16.2 How widespread is Doping Abuse in Recreational Sports?
We do not have a definite answer to this question for the same reason that we do not have a definite answer to the question of how widespread doping is in competitive sports. Doping is nearly always a secret, almost an occult activity. To document such an activity, one needs proof, for example, in the form of data from urine analysis. Proof like this was available in an Austrian study published in 1993 (Roggla et al. 1993), which showed that 2 to 7% of mountaineers climbing the Alps above 2500 m used amphetamines to boost their performance. Such studies, however, are rare.

If proof is not available, one has to resort to testimony, which can come from interviews, self-answered questionnaires or anecdotal reports. Testimony, however, is not always sincere. Even if confidentiality is guaranteed (e.g., through self-administered and anonymous surveys), people may not be willing to tell the truth. A body-builder with a distorted psychological profile (one often encountered among users of banned substances) may be suspicious that his/her identity could somehow be revealed, therefore he/she conceals the facts. Conversely, a youth considering doping fashionable may want to brag, therefore he/she falsely reports having used such substances.

With these limitations in mind, one could give some approximate figures. The incidence of doping among recreational athletes in the European Union and the United States has reportedly risen sharply during the past two decades from about 5 to over 20%. The percentage of male abusers is 3 to 7 times higher than that of female abusers. Of all the possible recreational sporting activities, body-building draws the lion share in doping. Reports raise the percentage of male body-builders having taken banned substances at least once, to between 20 and over 50, while the corresponding percentages among female body-builders range between 3 and over 10. However, when it comes to participants in body-building contests (which should be viewed like beauty contests rather than true athletic competition), nearly all appear to dope.

16.3 How aware is the Public of Doping Abuse in Recreational Sports?
Not greatly. While preparing for this presentation, I ran across the minutes of a session of the Irish Parliament in 1998, which were available through the Internet. While debating over amendments to the Irish Sports Council Bill, a senator says:

• “It is difficult to imagine doping in recreational sports. Doping is something which competitors engage in to enable them compete against each other to a higher level and succeed in competitive sport... Part of the importance of recreational sport is that there have never been any instances or allegations of doping.”

Another senator answers:

• “The biggest indication that dope is being used is in recreational sports. More people in gymnasiuums, participating in recreational sport, are using drugs than in competitive sports. I do not condone the use of drugs for any reason in the competitive area. However, men and women in gymnasiuums who lift huge weights are on some sort of drug to enhance their body-building capabilities. They are not engaged in competitive sports and only want to look better than others, although my view is that they begin to look horrible. The use of drugs in competitive sports arose from body-building in gymnasiuums. The drugs used by the big bodied hulks of men and women who competed in the Olympics in the past developed from drugs used in recreational sports. It is not that people in gymnasiuums are using drugs because of what happened in competitive sports.”
The first senator concedes:

- “I was not aware that banned substances were being used in gymnasiums...”

I don’t know whether there is any exaggeration in the second senator’s words, but if a member of Parliament who has been apparently assigned by his Party to discuss a sports bill is oblivious to doping in gyms, then one cannot blame the public for ignoring the problem. What’s more, one cannot expect people to make a distinction between the estimated prevalence of doping in elite sport and recreational sport. Indeed, a recent survey of public awareness in Switzerland revealed that doping in elite sport was perceived as a serious problem by 84% of the respondents, as opposed to 44% for recreational sport.

16.4 What is the Profile of the Recreational Athlete using Doping Substances?

Published studies and our own data indicate that the typical recreational athlete engaged in doping is a young male body-builder, who has a high school education, works in an office, and is single. He uses mainly anabolic androgenic steroids and obtains them from the black market (see tab. 1).

<table>
<thead>
<tr>
<th>Profile of the recreational athlete using doping substances:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Young male body-builder</td>
</tr>
<tr>
<td>o High school education</td>
</tr>
<tr>
<td>o Office worker</td>
</tr>
<tr>
<td>o Single</td>
</tr>
<tr>
<td>o He uses mainly anabolic androgenic steroids</td>
</tr>
<tr>
<td>o He obtains them from the black market</td>
</tr>
</tbody>
</table>

16.5 What do Recreational Athletes use Doping Substances for?

Contrary to competitive sport, performance enhancement is obviously not the prime reason for doping in recreational sport. The motive most often reported is improvement of appearance through muscle build-up and, less often, fat loss, followed by increase of strength (see fig. 1).

<table>
<thead>
<tr>
<th>What do recreational athletes use doping substances for?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faster recovery</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Muscle build-up</td>
</tr>
<tr>
<td>Increased strength</td>
</tr>
<tr>
<td>Allow harder training</td>
</tr>
<tr>
<td>Fat loss</td>
</tr>
</tbody>
</table>

The ability to train harder and recover faster between training sessions, as well as increased recovery from injury are also cited as reasons for doping.

16.6 What Substances do they use?

As in competitive sports, steroids are the best-selling illicit substances in recreational sports. Over 50% of users take both oral and injected preparations; of the remaining, more take only oral than only injected steroids. Both forms entail health risks: oral steroids are associated with liver toxicity, while injection with contaminated syringes may transmit diseases, such as hepatitis and AIDS. Substances used include testosterone esters, nandrolone decanoate (deca-durabolin), methandrostenolone (dianabol), metenolone enanthate (primobolan), stanozolol (winstrol, stromba), oxandrolone (anavar) etc.
Most recreational athletes using steroids do so in “cycles” interspersed with periods of abstinence. Such practice is said (although not proven) to maximize gains while minimizing side effects. Periods of use and abstinence last about 9 weeks each. The vast majority of users take more than one drug during a cycle (a maximum of 16 has been reported). This is called “stacking”. Another favorite practice is “pyramiding”, that is, gradually increasing the dose toward the middle of the cycle and then tapering it back down toward the end. (Again, there is no scientific proof that this administration scheme is more effective than, say, a fixed dose throughout the cycle).

Average doses of steroids used by men in gyms exceed the recommended therapeutic doses by approximately one order of magnitude. However, you have to multiply this by the number of drugs used at the same time to get the complete picture. Total dosages can reach or exceed 2000 mg per week. Women are more conservative, because their natural levels of steroids are much lower than those of men, therefore lower doses are required to produce a supra-physiologic response. So, the doses of steroids taken by women are usually close to the therapeutic ones, but, again, stacking has to be taken into account.

In addition, to steroids, recreational athletes take ephedrines and amphetamines for their stimulatory and lipolytic (fat dissolving) action, human chorionic gonadotropin to prevent testicular atrophy, clenbuterol, human growth hormone, and insulin for their anabolic potential, as well as antiestrogens to prevent gynecomastia (female breasts).

16.7 Who provides them with banned Substances?

The black market, fellow athletes, and trainers are the most frequently mentioned sources of doping substances. Generally, it is becoming increasingly easy to obtain doping substances in the era of globalisation. What raises additional concern here is that many users have no knowledge of what they are taking. There is a lot of counterfeits and fakes out there. There are illicit supply networks and manufacturers with poor quality control that distribute preparations of questionable content and purity.

16.8 What Side Effects do they report?

Side effects reported by recreational athletes who use doping substances are similar to those reported by competitive athletes and include testicular atrophy, fertility problems, acne, high blood pressure, gynecomastia, loss of hair/baldness, kidney problems, liver problems, body hair growth (mostly by females), deepening of voice (mostly by females), menstrual irregularities, and clitoral enlargement. It should be pointed out, however, that most abusers are not convinced that doping causes health problems. Evidence for long-term adverse effects is scarce and relatively few deaths have been firmly linked to doping. Many side effects seen in users of doping substances may just not be due to these substances. On the other hand, effects, such as high blood pressure, kidney problems, and liver problems, are not accessible to self-diagnosis and may go unnoticed.

16.9 What can we do about it?

Although limited, the available scientific data shows that doping abuse is a serious problem in recreational as well as in competitive sports. Both areas share high rates of increase in the number of users and similar patterns of substances used, regimens, procurement and side effects. Two special features of doping in recreational sports are additional cause for alarm:

- There is no doping control, which could restrain abuse.
- Recreational athletes are not officially supervised by a doctor and few seek medical consultation.

To combat doping in the gym and in other places fostering recreational sport, education should be our first weapon. As mentioned above, doping abusers are skeptical of health warnings. This, combined with the obvious physical benefits from using steroids and other banned substances, makes the vast majority of users unwilling to stop use. In a preliminary study, some interviewees defended their doping practices by arguing that smoking is a better established health problem, yet huge numbers of people do not quit! Such attitudes make it imperative to spread the scientific knowledge about the side effects and convincingly inform interested parties of the potential risks of doping. Scientists in related fields should organize educational campaigns like the present symposium, so that nobody can say they weren’t warned.

Additionally, as pointed out by Korkia and Stimson (1997), doctors and other health care professionals should be aware that some of their patients (and not only elite athletes) may be taking doping substances without revealing it. This may be important in avoiding misdiagnoses (for example, steroid use may lead to derangement of plasma lipids, decreased sperm count, and increased blood pressure) and consequent treatment which may prove ineffective.
Another important issue is that doping abusers should be convinced to undergo regular health checks, such as testing for blood lipids, liver function and blood pressure. The majority of doping users do not do so.

Finally, legislators and law enforcement agencies should do whatever is within their power to impose stricter control on the trade of banned substances at both national and European level in hope of curbing the modern epidemic of doping.

16.10 References


16.11 Questions

Question: What would you consider as the most serious problem associated with doping in recreational sports?

Answer: Since unfair competition is not an issue in recreational sports, I would not hesitate to point at the health risks as the most serious problem, especially in view of the fact that, as I said, many abusers are not supervised by a physician and don’t take regular health checks.

Question: What is the most important message that you would like to send to the public regarding doping in recreational sports?

Answer: The public should be aware that athletes practice doping not only for distinction in competition, but for a multitude of other reasons, including just looking better or feeling better. Therefore, doping is more widespread in our society than most people think. The fellow next door or a close relative might be a doping abuser. Realizing this is the first step towards being prepared to deal with it.

16.12 Address

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17 The Doping Trade: an exploratory Study into the Trade of performance enhancing Drugs in the Netherlands

A.W.A. Koert and Rens van Kleij

17.1 Introduction

In response to the media attention on athletes’ use of biologically derived growth hormone, written questions were submitted to the Dutch Minister Borst-Eijlers of Public Health, Welfare and Sports (VWS) concerning the increasing use of anabolic steroids. Due to the lack of information on the manner in which performance enhancing drugs (PEDs) are brought into circulation, her response to questions from the Dutch Parliament was to ask NeCeDo (The Netherlands Centre for Doping Affairs) to conduct an exploratory study in regard to the situation.

It was decided to limit the study to the largest group of doping users: athletes who work out at fitness centers and gyms. The emphasis of the study came to be the “illicit supply” of performance enhancing drugs on the “black market”. The study concerns the substances, users, sources and dealers. The dealers have received the most emphasis.

17.2 Method

A qualitative research strategy was chosen in order to map out the market for performance enhancing drugs. This choice was based on the illegal nature and negative connotations of the subject matter. Information was gathered from the following sources: publications from the cosmetic sports field (especially body-building magazines, but also autobiographical material), journalistic work, and previous studies on the use of performance enhancing drugs (both in the Netherlands and other countries). The main source of information, however, consisted of the various interviews conducted. To gather information, interviews were conducted with users (n=35) and dealers (n=11) of performance enhancing drugs, and key figures in the world of body-building and other sports (n=16). In addition, various interviews (n=11) were conducted with criminal investigators, for instance at the National Criminal Intelligence Service (CRI) division, customs, the Health Care Inspectorate, the Economic Surveillance Department (ECD) and private detectives working for agencies such as the Pharmaceutical Security Institute (PSI) who lend a hand to the pharmaceutical industry. Besides these groups, interviews (n=14) were conducted with physicians, journalists, researchers and representatives of the pharmaceutical industry. The information thus gathered was checked, organised and incorporated into this study.

17.3 Results

17.3.1 Substances

The core of the performance enhancing drugs used in fitness and gym circles consists of the “classic” anabolic steroids that were developed in the 50’s and 60’s. Anabolic steroids, or, as they are officially called, androgen anabolic steroids, are modifications of testosterone, the male sex hormone, and can be divided into dozens of types of chemicals. Different versions of virtually every kind of anabolic steroids (different dosages and manufacturers) are available in the fitness circuit and can range on a scale from “relatively mild” to “relatively aggressive”. Almost all users of performance enhancing drugs in fitness circles take one or more of these products, often in combination with other substances, which are used to control the side effects of the anabolic steroids, to augment the desired effect of the anabolic steroids or to burn off unwanted fat. The first category of these additional substances would include the so-called “activators” (such as clomiphene citrate or clomid), diuretics, corticosteroids or anti-estrogens (such as tamoxifen or nolvadex). The second category includes substances such as growth hormone, insulin and IGF-1. Substances that would fall in the third category include thyroid hormones, clenbuterol and amphetamine-based weight-loss formulas (such as fentermine or fenfluramine).
17.3.2 Users

The users of performance enhancing drugs can be divided into five different categories.

*Type 1 users*: the conservative, careful users who limit their consumption to infrequent use of tried and tested drugs like anabolic steroids, and who only use “light” dosages. These users “only” spend about 500 Euros on performance enhancing drugs a year.

*Type 2 users*: the conservative, large-scale users, who do not go beyond the classic, tested drugs (anabolic steroids), but who take these frequently, in high dosages. People in this category also tend to use more aggressive steroids. These users spend about a few thousand guilders (Dutch currency; 1 Euro = 2.2 NLG) a year on performance enhancing drugs.

*Type 3 users*: the experimental and careful users, who use the more experimental drugs in addition to anabolic steroids, such as growth hormone, insulin and IGF-1, but who use these fairly infrequently and in low dosages. These users generally spend thousands and thousands of guilders on performance enhancing drugs every year.

*Type 4 users*: users who do not balk at using both classic and more experimental drugs frequently and in high dosages. These users spend tens of thousands of guilders a year on performance enhancing drugs.

*Type X users*: users of amphetamine-based weight-loss formulas who don’t use anabolic steroids. Initially, these products were used primarily by female cosmetic athletes, who wanted to lose body weight by taking drugs such as fentermine purchased on the black market, and who do not use other drugs. According to dealers, users and key figures in the fitness world, trade in these drugs is extending to groups who have nothing to do with the fitness and gym circuit. The trade in weight-loss drugs could also be occurring in certain cafes, for instance. This category of users of performance enhancing drugs does not match any of the four types mentioned above, so this group is called “Type X”.

17.3.3 Trends

Many users, dealers and key figures who were approached as part of this study point to clear trends in use: on the one hand, dosages are rising, while on the other hand, there is increased acceptance of the more experimental drugs. Substances like growth hormone, amphetamine-based weight-loss formulas and clenbuterol have come within reach of larger groups of users, and have come to be regarded as “normal standard drugs” among a relatively large group of athletes over the past decade. According to those interviewed, there is a “pill-popping mentality”, suggesting a lowered threshold of acceptance for substances that are foreign to the body.

17.3.4 Predictors of use

Three factors can be identified which prompt athletes to use performance enhancing drugs. Firstly, there is the dream of having the perfect body, at least as perceived by members of the fitness circuit. The desire for that perfect body is much stronger to many than their fear of the risks, and outweighs the financial sacrifices that must be made. Secondly, there is a correlation between being acquainted with someone using performance enhancing drugs and beginning to use or being interested in using such substances oneself. It seems that knowing users is a prerequisite for being able to obtain these substances. Thirdly, previous use of performance enhancing drugs appears to be an important factor for repeated use. This seems to be due in particular to the fear of losing muscle mass and strength.

17.3.5 Dealers

Most of the consumers buy performance enhancing drugs from dealers. It is very rare now for any of them to receive the substances from (sports) physicians. Physicians have been officially prohibited from providing medicines for doping purposes since 1995. Nonetheless, there are still a few who do not take much notice of the law. They contribute very little to tipping the scale, though, when compared with the dealers discussed below.

Dealers of performance enhancing drugs who operate in the Netherlands can be divided into categories. In the Netherlands, as far as we know, there are a dozen major dealers who actively deal in performance enhancing drugs. These “big-time” dealers can be divided into two smaller categories:

- The dealers who have built up an organisation around themselves, and
- The dealers who mostly work solo.

These two groups are called “organisations” and “solo operators” in this study. These big dealers sell a portion of their supplements directly to consumers, but foremost to other dealers. The organisations and solo operators
can also be seen as the primary port of entry through which performance enhancing drugs end up on the ‘black market’ in the Netherlands. The other dealers include relatively large-scale dealers (referred to as “second-tier dealers” below) and also “small-scale dealers”. Second-tier dealers sell performance enhancing drugs at their gym, or work as a “house dealer” in one or more gyms. It is estimated that there are a few dozen second-tier dealers in the Netherlands.

Small-scale dealers tend to be users themselves, who deal to defray the cost of their own use or who sell the performance enhancing drugs they have left over to friends and acquaintances.

Total annual sales of performance enhancing drugs in the Netherlands are estimated to amount to at least 200 million guilders.

17.3.6 Sources

There are many people who claim that the pharmaceutical industry – the conglomeration of pharmaceutical companies, wholesalers and pharmacies – was the main source of performance enhancing drugs in the Dutch dealing network until the late 80’s. There are known cases where pharmacists, wholesalers and pharmaceutical manufacturers directly supplied to the “big-time” dealers. In almost all of the cases, these were foreign organisations. There are also cases of deliveries to small-scale dealers. These are almost always pharmacies located in a resort area where the sale of performance enhancing drugs (mostly medicines) is not as strictly regulated as in the Netherlands. There are indications that at least one Dutch pharmacy has engaged in the sale of performance enhancing drugs. This situation underwent radical changes in 1998, however. The market share of illegal producers on the black market for performance enhancing drugs has risen dramatically since the mid-80’s. At the moment, we can assume that the bulk of the drugs dealt in fitness circuit, originates from this group of producers. Insiders believe that 60 to 70% of all performance enhancing drugs are made by illegal producers.

These illegal producers come in all shapes and sizes. There are manufacturers that “cut” existing performance enhancing drugs obtained from the pharmaceutical industry, manufacturers of performance enhancing drugs containing no active ingredient or completely different active ingredients than indicated on the packaging. Finally, there are illegal manufacturers that actually produce the active ingredients that are indicated on the packaging of the contraband supplements itself.

The basic ingredients that are required come from three different sources:

- There are cut substances, obtained from the pharmaceutical industry;
- There are ready-made active ingredients and fillers that are obtained from the pharmaceutical industry and then pressed into tablets or capsules; and, finally,
- There are illegal labs where the active ingredients are produced completely independently.

Most of these labs are located in countries with a rudimentary legislation concerning pharmaceuticals, such as Thailand, Nigeria, India and Vietnam. Criminal investigation agencies have reason to believe that illegal production of performance enhancing drugs also occurs in the Netherlands.

The illegal produced performance enhancing drugs are partially sold under the name of an existing brand. That constitutes fraud. The drugs are also sold under fake brands. The “fake brands” and “counterfeit brands” can be found throughout the illegally produced supply. For instance, counterfeit versions of Organon’s deca-durabolin are in circulation, which either have absolutely no active ingredients or nandrolone decanoate or completely different active ingredients altogether.

In certain cases, these are operations that are part of the drug world; in other cases, people who make performance enhancing drugs also make counterfeit versions of other kinds of drugs.

The replacement of authentic products by products from illegal manufacturers has gone hand in hand with the rise of international (criminal) organisations of dealers in performance enhancing drugs since the 80’s. Their market function is two-fold: in certain cases, these kinds of organisations deal in performance enhancing drugs produced by the pharmaceutical industry, and in others, organisations produce the drugs themselves. They are also active in the Netherlands and supply large-scale dealers. This study has not revealed any cases in which these international organisations supplied second-tier dealers, small-scale dealers or consumers themselves. A number of Dutch organisations have grown to become established international organisations. In other words, the processes of “globalisation” have not passed by the doping trade.

The study revealed that there are a number of users in the Netherlands who buy performance enhancing drugs from the internet. A substantial number of dealers are now active on the internet. The majority of these are “mail-order businesses” that use the Internet as their medium. In most of the cases, these mail-order businesses buy their goods from the pharmaceutical industry. In other cases, these are dealers who are active newsgroups and bulletin boards specifically geared towards fitness, body-building and weight-lifting.


17.4 Conclusions

Based on interviews mostly with representatives of the cosmetic sports world, the conclusion that can be drawn is, that the use of performance enhancing drugs is worrisome. There are three reasons:

4. First of all, the use of performance enhancing drugs has apparently spread over the years to groups who didn’t formerly use them.
5. Secondly, athletes more readily turn to performance enhancing drugs than they did in the past, using higher dosages and riskier substances. The people interviewed for this study spoke of a “pill-popping mentality”.
6. The third reason for concern is the increase in the number of counterfeit brands on the market for performance enhancing drugs and the concomitant drop in quality.

What we know about the trade in these substances gives rise to the same conclusion. There is an extensive national and international network engaged in the trade and production of performance enhancing drugs. This network is exhibiting new, risky developments. We are referring on the one hand to the degree with which this network is intertwined with other criminal networks and everything that goes along with that (threats, intimidation, drug-related murders). In addition, as mentioned above, this has a detrimental effect on the quality of the products dealt out on the black market.

17.5 Recommendations

There are lenient laws in the Netherlands that could be enforced to prosecute illegal producers and dealers of performance enhancing drugs. There are also investigation services, such as the Health Care Inspectorate and the Economic Surveillance Department, that have some resources, authority and expertise in this area. Yet interviews with inspectors and detectives revealed that the Justice Department’s policy is to drop charges against those charged with the illegal trade and production of performance enhancing drugs. This policy may have been justified in the mid-80’s, but is no longer justifiable. Legal action where excesses concerning the illegal production and trade of performance enhancing drugs are apparent, is therefore recommended. In addition, the formation of a task force which brings together expertise, resources and focus on this matter is recommended. This task force should give priority to the tracing and persecution of producers of counterfeited performance enhancing drugs, as well as the pin-pointing and stopping up of “leaks” in the supply of pharmaceuticals.

Next to that this task force could function as an (inter)national contact point about performance enhancing drugs. Finally, it is recommended to register all known performance enhancing drugs in a database that could be consulted by all police departments.

17.6 Address

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18 Is the present Doping Definition still appropriate?

Harm Kuipers

18.1 Introduction

The IOC takes a strong stand against doping and plays a leading role in the anti doping policy of international sport organizations. The IOC produced a list of forbidden substances, and doping is by definition everything that is on that list (IOC 1996). The IOC list of banned substances is reviewed almost yearly and there is a strong tendency to enlarge the list every year. Because the rationale for putting certain substances on the doping list can be challenged, lawsuits of victimized athletes will probably become more frequent.

It appears that in the fight against doping some important aspects are overlooked, such as the basic question why doping is forbidden. The basic reasons for banning doping are:

- Unfair competition,
- Health problems and
- Non-sportive behaviour.

An aspect of the doping regulations that should be realized is that the doping list in itself may stimulate doping use. Many athletes and people counseling athletes have the strong conviction that everything on the doping list must have a performance enhancing effect. Therefore, the doping list is also considered as a shopping list for athletes and coaches. A recent, regrettable step of the IOC was to add insulin to the doping list. Unfortunately, the knowledge of coaches is often overestimated and putting insulin on the list may encourage coaches and athletes to use it. This may lead to accidents because in athletes the insulin sensitivity is increased and therefore insulin injections may lead to an uncontrollable, life threatening hypoglycemia. This is surely not the intention of the doping regulations.

18.2 Definition of doping

A first, but very important step in the doping issue is to define doping more clearly. A basic reason to forbid doping is unfair competition, assuming that the substances on the list are performance enhancing. The second reason for banning doping is to protect the athletes’ health. A third reason is that athletes should be an example for youngsters.

Thinking along the lines of the two main basic criteria one can argue that only agents with an established or likely positive effect on performance, plus additional serious risks for health should be forbidden. Among the general public and also in athletic circles it is not very well known that several substances on the list do not have any performance enhancing effect at all, and that some even have a negative effect on sport performance. All the agents that do not meet these two criteria can seriously be questioned. Just the fact that athletes use certain substances is no reason in itself to ban them. By leaving such substances on the list, the assumption that these agents are performance enhancing is strengthened and this may encourage some athletes to use them.

On substances like EPO, blood doping, androgenic anabolic steroids (ACSM 1987), there is little discussion whether they should be forbidden or not. These substances have been shown to have ergogenic effects and may have serious health risks as well (ACSM 1987, Brien and Simon 1987, Ekblom and Berglund 1991, Kuipers et al. 1991, ACSM 1996). One of the substances that needs further investigation is growth hormone. Although growth hormone appears to be used by several athletes, no study has shown any performance enhancing effect in any sport in healthy persons (Yarasheski 1994). On the contrary it is likely that hGH in healthy subjects may lead to performance decrements. Still they are widely used, probably because they are on the list, and because its use cannot be detected yet.

A group that can seriously be questioned following the two basic criteria is the group of narcotics. These strong pain killers have certainly a negative effect on sport performance, although specific research on the effects of these substances on sport performance are lacking. So it would be very unwise of a doctor to prescribe these and for an athlete unwise to take drugs out of this group before training or competition. If an athlete wants to use them or if a doctor wants to prescribe them, it is the responsibility of the physician. Sometimes the argument for putting this group on the list is that it may have serious side effects. However, putting substances on the list just because of serious side effects has little to do with unfair competition and should not be a reason to forbid them in sport. One should realize that for instance boxing, skiing and downhill cycling involves significantly more direct life threat than taking certain forbidden substances.
One of the substances that can also be questioned is caffeine. All the research that has been done has shown that caffeine is ergogenic, however there are no serious health risks involved (Pasman et al. 1995). Above a dose of 5 mg/kg there is no additional effect on performance, whereas the risk for negative effect on performance and a positive urine increase (Pasman et al. 1995). Another problem with caffeine is that there is an inter-individual difference in caffeine handling and clearance. Because everybody has free access to caffeine, there is no unfair competition or serious health risk. There is, however, an unfairness in the detection since inter-individual differences in caffeine handling may make the urine of one athlete positive while the same intake may yield a negative urine in another athlete.

In 1999 insulin was added to the list of banned substances. The motivation for adding insulin to the list with banned substances is probably the assumption that insulin may act as recovery enhancing means. However, there is no scientific basis for this assumption. Just the fact that insulin is on the list may encourage people to use it because of the assumed recovery-enhancing properties. This in turn may lead to uncontrollable hypoglycemia and death.

There are still several substances that need further research to assess the effects on sport performance. If there is any theoretical basis for a possible performance enhancing effect such substance should be maintained on the list until conclusive evidence is available.

One of the substances that is not on the doping list, but that is questioned by some is creatine. Although in the laboratory a decreased fatigability of repeated bouts of anaerobic exercise have been shown, there is no proof that it will increase performance of single bouts of exercise such as the 100 meter dash (Mujika and Padilla 1997). In addition, creatine is also present in normal nutrition, and there is no evidence at all for any health threat (Poortmans and Francaux 1999). Most probably the wave of creatine will wane. However, if it were added to the list, this would rather increase its use. If it were added to the list, a special problem that would have to be solved is the detection methodology and the allowed intake. It has to be realized however, that the same effect on performance can be obtained by low doses over a longer period of time, compared to high doses over a short period of time.

A recent reason to forbid certain substances like marijuana, is that athletes should be an example for young people. These substances are generally not performance enhancing, and because they temporarily effect brain function everyone should be advised not to use these substances. However, forbidding these substances has no relevance for sport performance and means that officials dictate athletes how to behave outside the sports arena and this appears to be a violation of individual human rights. Social problems and misconduct by athletes should not be solved via the doping rules, but by other means.

If the basis for putting substances on the doping list or not were more straight forward and based on clear and defendable criteria, things would be easier for the athlete, the doctor and the doping control.

### 18.3 Doping control

If the doping list were shorter, the doping laboratories would only have to focus on the substances that are still on the list for good reasons. This may decrease the costs of single tests, enabling to increase the number of tests. The abuse of EPO can be fought via screening of blood, combined with targeted blood and urine collection.

### 18.4 Epilogue

Doping has no place in sport, because there is a general consensus that the use of methods or drugs that involve serious health risk, and are performance enhancing, is not allowed. It is an illusion to assume that the doping problem will be banned completely, however, a first step may be to better define doping. In addition, teaching programs for athletes and coaches, and appropriate penalties may contribute to win the fight against doping in sport.

### 18.5 References


18.6 Questions

Question: What is your definition of doping?

Answer: My definition of doping is still everything listed on the IOC list but meeting two criteria: performance enhancement plus serious health risks.

Question: You mentioned a number of compounds that should not be on the list or should be questioned because they are not performance enhancing but a number of these compounds may enable the athlete to stand a painful training.

Answer: There have been some studies. If you use social drugs "marijuana" your performance goes down. You may be euphoric to a small extent, but your performance deteriorates, decreasing your stimulus to train. Another example is heroin morphine: people may be a little euphoric but they are not able to maintain the high intensity training they need for an adequate training response. I think there are very few substances which really enhance the training ability. Some people even say that of anabolic steroids: there are some indications that there may be some enhancement of recovery. Although we have been working on aspects of recovery for about 25 years, we still do not know most of the answers. It is more complicated than it appears at first sight. But the ultimate question is: is there any performance enhancement? Further most of the substances even substances which may cause some changes in mental states, do not lead to a performance enhancement.

Question: Your criteria that both performance enhancement “and” health risks must be substantiated before you put it on the list is quiet questionable and you might remember that especially in the last anti doping list an “or” was put instead of “and”. So my question is: why are you so firm in claiming that you need the clear substantial performance enhancement proved and the health risks? I believe an “or” is better and if you require performance enhancement proved you will never have designer drugs as for example bromantan. I wonder if you would have the plasma expanders. I agree with you that there might be a different opinion among other colleagues working in the field.

Answer: Of course I realise that, also I could challenge that. If we have the or-or criteria. There are substances which are not performance enhancing. For instance heroin morphine, of course there are serious health risks. But why use it? By putting it on a list we should realise that this suggests to people that it is performance enhancing even if we maintain other reasons for enlistment. The result will be that people will use them. So why are we talking about doping? Why do we want to ban doping? We want to prevent unfair competition in the first place, and we also want to protect the health of the athletes. So if we have the or-or criteria there still remain many substances on the list which have no performance enhancement at all. They may even impair performance but still by being on the list it may stimulate the user. I think the or-or will not aid us in this respect. I think we should take firm steps now and encourage discussions on this issue. Of course there should be consensus on how we define health risk – headache? I think many people will not agree that there are serious health risks so we should also agree on these substances.

Question: Altitude training is a very complex problem involving many factors. Can you comment on this in more detail?

Answer: Altitude is a very interesting point. Since the Olympic Games in Mexico City in 1968, a lot of research has been conducted. The studies show that athletes living at high altitudes for many weeks acclimatise for performance at altitude. Yet no increase of performance at low altitudes is accomplished. A further fact is that
no world record was broken in the year of 1968. Thus altitude training as proven by most studies, does not lead to any performance enhancement, it might even lead to a performance decrement.

Question: What do you think about the theoretic possibility to permit all substances which are medically indicated, and to ban everything else which is not reasoned by medical treatment?
Answer: Of cause an athlete is permitted to use certain listed drugs when they have a medical notification. There should be research whether there is any performance enhancement, because there is even a discussion arising with regard to β-agonists. For example why performance enhancement occurs in healthy well trained high elite athletes, or regarding performance enhancement in athletes beyond the normal level. I think we have good points to ask for other medication. That is one of the important points for further discussion.

18.7 Address

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