BIOMEDICAL SIDE EFFECTS OF DOPING!
HIGH LEVEL

The High-Version of the teaching material assumes a basic knowledge in the field of doping substances. The material focuses solely on the side effects in the human body. If basic knowledge on the topic of doping prevention is desired the Basic and/or Medium-Versions of the teaching material should be worked over first.

Furthermore, we would like to mention and recommend that the Congress Manual "Biomedical Side Effects of Doping" contains detailed information beyond this script that can also be used as background information for the High-Version presentation.

Free download of Congress Manual:

www.dopingprevention.sp.tum.de/index.php?id=45

SLIDE 2:

The World Anti-Doping Agency (WADA) describes the World Anti-Doping Code as follows:

“One of the most important achievements to date in the fight against doping in sport has been the drafting, acceptance, and implementation of a uniform **set of anti-doping rules**, the World Anti-Doping Code (Code). The Code is the core document that provides the **framework for harmonized anti-doping policies, rules, and regulations** within sport organizations and among public authorities. It works in conjunction with four International Standards aimed at bringing harmonization among anti-doping organizations in various areas: **testing, laboratories, therapeutic use exemptions (TUEs) and the List of Prohibited Substances and Methods**. …”.

The complete description and the whole document can be downloaded at http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=250.

Picture shows: Global structure of the anti-doping policy by the World Anti-Doping Agency according to the World Anti-Doping Code.

- **WADA and the World Anti-Doping Code (“The Code”)**
  ➔ international, independent monitoring regulator/watchdog of the global fight against doping in sport and its framework (“The Code”).
- **IOC (International Olympic Committee), IPC (International Paralympic Committee), IF (International Sports Federations)**
  ➔ responsible for the testing process and the sanctioning. National Federations often fulfil this role.

- **Governments**
  ➔ financial, political and structural support and much more.
- NOCs (National Olympic Committees), NPCs (National Paralympic Committees), NFs (National Sports Federations)
  ➔ should agree to implement the Code.
- **NADOs (National Anti-Doping Organisation), RADOs (Regional Anti-Doping Organization)**
  ➔ responsible for testing national athletes in- and out-of-competition and adjudicating anti-doping rules violations and anti-doping education.
- **Athletes and Entourage**
  ➔ complying with the Code.
- **LABs (Laboratories)**
  ➔ analyse doping control tests.
- **CAS (Court for Arbitration for Sports)**
  ➔ facilitate the settlement of sport-related disputes.

SLIDE 3:

According to the World Anti-doping Code the following rule violations are defined:

2.1 **The presence of a *Prohibited Substance*** or its *Metabolites* or *Markers* in an *Athlete's* bodily Specimen

2.2 **Use or Attempted Use of a** Prohibited Substance or a Prohibited Method.

2.3 **Refusing, or failing** without compelling justification, to submit **to *Sample* collection** after notification as authorized in applicable anti-doping rules, or otherwise evading *Sample* collection.

2.4 **Violation** of applicable requirements regarding *Athlete* availability for ***Out-of Competition Testing*** including failure to provide required whereabouts information and missed tests which are declared based on reasonable rules.

2.5 *Tampering*, or *Attempting* to tamper, with any part of *Doping Control*.

2.6 Possession of Prohibited Substances and Methods…

2.7 Trafficking in any Prohibited Substance or Prohibited Method.

2.8 **Administration** or *Attempted* administration **of a *Prohibited Substance*** or *Prohibited Method* to any *Athlete*, or assisting, encouraging, aiding abetting, covering up or any other type of complicity involving an anti-doping rule violation or any Attempted violation.

The 2003 World Anti-Doping Code and its originally content is available under: http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=250.

SLIDE 4:

The "Prohibited List" of the World Anti-Doping Agency is arranged as follows:

Substances prohibited at all times (prohibition in- and out-of-competition)

S1. Anabolic agents

S2. Hormones and related substances

S3. Beta-2 agonists

S4. Hormone antagonists and modulators

S5. Diuretics and other masking agents

Methods prohibited at all times (prohibition in- and out-of-competition)

M1. Enhancement of oxygen transfer

M2. Chemical and physical manipulation

M3. Gene doping

Substances and methods prohibited in-competition

S6. Stimulants

S7. Narcotics

S8. Cannabinoids

S9. Glucocorticosteroids

Substances prohibited in particular sports

P1. Alcohol (e.g. prohibited in archery, automobile sports, motorcycling et al.)

P2. Beta-blockers (e.g. prohibited in bobsleigh, skiing and snowboarding [jumping, freestyle, halfpipe], wrestling)

The list is updated and published annually. The currently available Prohibited List can be downloaded under www.wada-ama.org/en/dynamic.ch2?pageCategory.id=370.

SLIDE 5:

The Anti-Doping rule compliance is controlled by testing procedures encountering all athletes within special testing pools. **International sports federations** should build a **testing pool for their international level athletes**, whereas **national anti-doping organizations** should create a **registered testing pool for national athletes**. The testing procedure is a so called “target testing”, meaning athletes aren’t randomly chosen. Furthermore, there is an **in-competition** testing (for substances and methods prohibited in-competition) and an **out-of-competition** testing (for substances and methods prohibited out-of-competition).

The testing procedure is divided into two ways. One is the **advance notice test** and the other one is the **no advance notice test** which should be preferred. If a test is

announced it should take place within no more than 6 hours after warning. In the case of a no advance notice test less than one hour should pass after approach. Within this hour the tested athletes should be under constant supervision.

The 2003 World Anti-Doping Code and its original content about the testing procedure is available at:
http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=250.

SLIDE 6:

Doping control samples may be urine samples or blood samples, although the WADA code allows for the collection of other biological samples (hair, saliva, etc) as well. Most samples are still urine samples. However, more and more blood samples (two A- and B-samples of three millilitres of blood) are taken to control the absence of prohibited substances or methods.

Today most blood samples are used for the control of the athlete's health status (e.g. increased haematocrit in cross-country skiing ⇨ higher risk of arterial hypertension and thromboembolic events).

SLIDE 7:

According to the Therapeutic Use Exemption Guidelines of the WADA the definition is as follows: A Therapeutic Use Exemption (TUE) is an **authorization to take a Prohibited Substance under well defined and restricted conditions**. An application for a TUE shall be made in accordance with the International Standard for TUE. A TUE must be obtained for the use of any Substance on the Prohibited List. Depending on the Substance itself and the route of administration …, either a standard TUE or an Abbreviated TUE (ATUE) can be granted. All athletes who need a medical treatment including a Prohibited Substance or Method and are subject to Testing must obtain a TUE from their relevant Anti-Doping Organisation (ADO). In order to obtain an approval for a TUE, athletes must have a well documented medical condition supported by reliable and relevant medical data.

The four criteria that need to be fulfilled to grant a TUE are stated in the International Standard for TUE:

1. The athlete would experience a **significant impairment to health** if the Prohibited Substance or Prohibited Method were to be withheld in the course of treating an acute or chronic medical condition (Article 4.2 International Standard for TUE).

2. The therapeutic use of the Prohibited Substance or Prohibited Method would produce **no additional enhancement of performance** other than that which might be anticipated by a return to a state of normal health following the treatment of a legitimate medical condition. The use of any Prohibited Substance or Prohibited Method to increase “low normal” levels of any endogenous hormone is not considered an acceptable therapeutic intervention (Article 4.3. International Standard for TUE). Under 'enhancement of performance' should be understood: the return by the athlete to the level of performance possessed before the treated medical condition occurred. It means that a certain enhancement of individual performance, due to the efficacy of the treatment, can occur, but that it cannot go beyond the level of performance of the athlete prior to his/her medical condition.
3. There is **no reasonable therapeutic alternative** to the use of the otherwise Prohibited Substance or Prohibited Method (Article 4.4. International Standard for TUE). Two points for reasonable therapeutic alternatives must be retained:
   - Only valid and referenced medications are considered alternative.
   - The definition of what is valid and referenced can vary in different countries. These differences should be taken into account, e.g. a medicine could be registered in one country and not in another, or still be under testing, etc.
4. The **necessity for the use** of the otherwise Prohibited Substance or Prohibited Method cannot be a consequence, wholly or in part, of prior non-therapeutic use of any substance from the Prohibited List (Article 4.5. International Standard for TUE). A TUE can only be granted if all four criteria are fulfilled.

The complete information on Therapeutic Use Exemptions (TUE) can be downloaded at: www.wada-ama.org/en/dynamic.ch2?pageCategory.id=373.

SLIDE 8:

Most doping substances are originally pharmaceutical drugs. These drugs are used for the medical treatment of a range of medical conditions. According to this aspect, these drugs have on the one hand their desired effects on the illness but on the other hand their undesirable side effects. These biomedical side effects are controlled and tested within several special trials and are proved to be acceptable in reference to the problems arising from the original illness.

The problem of the use of medical drugs as performance-enhancing substances is the fact that healthy athletes take drugs without an adequate necessity. And furthermore most substances abused are taken in so called suprapharmacological doses or in different combinations ("stacking") without prior medical investigation leading to biomedical side effects which no one can really predict.

Picture shows: The relationship between drugs used for **medical purpose** and drugs abused in sports. The medically used drugs show therapeutic effects within **pharmacological** doses, whereas performance-enhancing drugs could show **hazardous** effects cause of the usage in **suprapharmacological** doses. As a consequence the side effects can be **short-term, reversible, irreversible or result in delayed adverse effects**.

SLIDE 9:

- Overview of organic systems that are affected by an abuse of doping substances
- These systems will be discussed within this presentation:
    - Cardiovascular System
    - Blood and vascular system
    - Skin
    - Hepatic system
    - Musculoskeletal system
    - Endocrine system
    - Central nervous system
    - Immune system
- Gene doping will also be discussed briefly.

SLIDE 10:

Several biomedical side effects of the abuse of prohibited substances are expressed in the cardiovascular system. These biomedical side effects depend on the type of the consumed drug, as well as on the amount and duration of intake and the sensitivity of the body. There is a large inter-individual variability in responses to a drug. Usually the doses used in sports are much higher than those tested in clinical trials and used for therapeutic purposes. The abuse of several drugs in combination is frequent, leading to a higher risk of side effects. Among biomedical side effects of doping, the cardiovascular ones are the most harmful.

The prohibited substances with the highest rate of biomedical side effects on the cardiovascular system are (according to Deligiannis and coworkers):

Anabolic androgenic steroids (most effects) > cocaine > ephedrine, alcohol, amphetamines > hGH, beta-2-agonists > cannabinoids > glucocorticosteroids, erythropoietin > diuretics, narcotics (less effects).

These drugs lead to:

Arrhythmias > sudden cardiac death > hypertension > myocardial infarction > heart failure > coronary artery disease > left ventricular hypertrophy.

More detailed information can be found:

Deligiannis, Björnstad, Carre, Heidbüchel, Kouidi, Panhuyzen-Goedkoop, Pigozzi, Schänzer & Vanhees (2006): ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes; European Journal of Cardiovascular Prevention and Rehabilitation, 13:687–694.

SLIDE 11:

There are five different mechanisms discussed in relation to cardiovascular effects of prohibited substances. The first one is the **"atherogenesis mechanism"**. The atherogenic effects of anabolic androgenic steroid abuse are based on the lipoprotein profile. AAS intake can lead to a decrease of high-density lipoprotein (HDL) cholesterol and an increase of low density lipoprotein (LDL) cholesterol. These effects form the basis for atherosclerotic changes in the blood vessels. Consequently all this can lead to a higher risk of sudden cardiac death, arterial hypertension or thromboembolic events.

Upper picture shows: Hypertrophic coronary arteries with a hypertrophic media and broadened intima (EVG-colouration, 100:1 enlargement).

Lower picture shows: Former infarct with aneurysm and thrombus; inlay: ectasia of the right coronary artery.

More detailed information can be found:

Hartgens & Kuipers (2004): Effects of Androgenic-anabolic Steroids in Athletes; Sports Med, 34 (8): 513-554.

Tischer, Heyny-von Haußen, Mall & Doenecke (2003): Koronarthrombosen und -ektasien nach langjähriger Einnahme von anabolen Steroiden; Z Kardiol 92: 326-331.

Deligiannis, Björnstad, Carre, Heidbüchel, Kouidi, Panhuyzen-Goedkoop, Pigozzi, Schänzer & Vanhees (2006): ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes; European Journal of Cardiovascular Prevention and Rehabilitation, 13:687–694.

SLIDE 12:

There are five different mechanisms discussed in relation to cardiovascular effects of prohibited substances. The second one is described by the **"thrombosis mechanism"**. Anabolic androgenic steroids influence the haemostatic system. On the one hand they lead to an **increase of platelet aggregation**, thrombin and plasmin generation and on the other hand anabolic androgenic steroids lead to a decrease of fibrinolytic activity and synthesis of prostacyclin. Consequently, anabolic androgenic steroid abuse can increase the risk of cardiovascular events, e.g. angina pectoris disorders or myocardial infarction.

Picture shows: Coronary angiogram of the A. coronaria sinistra. 2 cm after outlet of RIVA (Ramus interventricularis anterior) lays a 3 cm long thrombus.

More detailed information can be found:

Hartgens & Kuipers (2004): Effects of Androgenic-anabolic Steroids in Athletes; Sports Med, 34 (8): 513-554.

Tischer, Heyny-von Haußen, Mall & Doenecke (2003): Koronarthrombosen und -ektasien nach langjähriger Einnahme von anabolen Steroiden; Z Kardiol 92: 326-331.

Deligiannis, Björnstad, Carre, Heidbüchel, Kouidi, Panhuyzen-Goedkoop, Pigozzi, Schänzer & Vanhees (2006): ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes; European Journal of Cardiovascular Prevention and Rehabilitation, 13:687–694.

SLIDE 13:

There are five different mechanisms discussed in relation to cardiovascular effects of prohibited substances. The **"coronary artery vasospasm mechanism"** is the third one. In general nitric oxide acts as an endothelial-derived relaxing factor in smooth muscles of arteries leading to vasodilatation. In this context anabolic androgenic steroids may inhibit nitric oxide which would probably provoke a vasospasm. In a worst case, this vasospasm could induce a cardiovascular ischemia or even an infarction.

More detailed information can be found:

Hartgens & Kuipers (2004): Effects of Androgenic-anabolic Steroids in Athletes; Sports Med, 34 (8): 513-554.

Deligiannis, Björnstad, Carre, Heidbüchel, Kouidi, Panhuyzen-Goedkoop, Pigozzi, Schänzer & Vanhees (2006): ESC Study Group of Sports Cardiology Position Paper

on adverse cardiovascular effects of doping in athletes; European Journal of Cardiovascular Prevention and Rehabilitation, 13:687–694.

SLIDE 14:

There are five different mechanisms discussed in relation to cardiovascular effects of prohibited substances. The fourth one is called the **"direct cell death mechanism"**. The growth stimulating effects of anabolic androgenic steroids can lead to a hypertrophy of cardiomyocytes with further consequences as disturbances of the anatomical structure. The increasing hypertrophy of the cardiomyocytes can reduce the arterial supply of oxygen. Furthermore, the cardiomyocytes show an increasing fibrosis with a decrease in cardiac performance.

More detailed information can be found:

Hartgens & Kuipers (2004): Effects of Androgenic-anabolic Steroids in Athletes; Sports Med, 34 (8): 513-554.

Deligiannis, Björnstad, Carre, Heidbüchel, Kouidi, Panhuyzen-Goedkoop, Pigozzi, Schänzer & Vanhees (2006): ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes; European Journal of Cardiovascular Prevention and Rehabilitation, 13:687–694.

SLIDE 15:

There are five different mechanisms discussed in relation to cardiovascular effects of prohibited substances. The last mechanism is described by **"degenerative changes"**.

Fineschi and coworkers (2006) suggested that cardiac arrest may be mediated by a catecholamine myotoxicity which could be associated with ventricular fibrillation due to myocardial necrosis and degenerative changes within the intramyocardiac sympathetic neurons.

More detailed information can be found:

Fineschi, Baroldi, Monciotti et al. (2001): Anabolic steroid abuse and cardiac sudden death: a pathologic study. Arch Pathol Lab Med, 125: 253-255.

Hartgens & Kuipers (2004): Effects of Androgenic-anabolic Steroids in Athletes; Sports Med, 34 (8): 513-554.

Deligiannis, Björnstad, Carre, Heidbüchel, Kouidi, Panhuyzen-Goedkoop, Pigozzi, Schänzer & Vanhees (2006): ESC Study Group of Sports Cardiology Position Paper

on adverse cardiovascular effects of doping in athletes; European Journal of Cardiovascular Prevention and Rehabilitation, 13:687–694.

SLIDE 16:

Two types of substances are mainly known to influence the vascular and blood system. On the one hand there is **erythropoietin and its mimetics** and on the other hand there are autogenic and allogenic **transfusions**. Accordingly, the biomedical side effects derive from changes of the blood consistency. Erythropoietin increases the amount of red blood cells, especially erythrocytes, and transfusion increases immediately the circulating blood volume. As a consequence the risk of deep vein thromboses, pulmonary emboli, coronary or cerebral thromboses or infectious diseases can be greatly increased.

SLIDE 17:

The slide describes the vascular system with its two parts: the arterial and the venous system. Both parts induce different clinical complications. A stimulated erythrocytosis increases red blood cells, haemoglobin and haematocrit levels which leads to increased blood viscosity and thrombogenicity. The arterial system can present cerebral and coronary thrombosis, whereas the venous system can show deep vein thrombosis and pulmonary emboli.

More detailed information can be found:

Jelkmann (2001): Beneficial and adverse Effects of Erythropoietin Therapy in Peters, Schulz, Michna: Biomedical Side Effects of Doping. Wissenschaftliche Berichte und Materialien des Bundesinstitutes für Sportwissenschaft 13; Sport und Buch, Köln 2001, p35-42. www.lrz-muenchen.de/~tc131ac/webserver/webdata/index.html

SLIDE 18:

The vascular system and the blood system provide the Oxygen(O_2)-supply of the whole body. Especially in stressful situations like endurance performances an adequate O_2-supply to the heart and the skeletal muscles is limiting. Several parameters are determining this endurance capacity. The O_2-supply depends on the maximal cardiac output and the maximal O_2-extraction. Especially an increased haemoglobin concentration leads to improved physical performance. Methods to manipulate this O_2-carrier are associated with biomedical side effects of the vascular system.

More detailed information can be found:

Jelkmann (2001): Beneficial and adverse Effects of Erythropoietin Therapy in Peters, Schulz, Michna: Biomedical Side Effects of Doping. Wissenschaftliche Berichte und Materialien des Bundesinstitutes für Sportwissenschaft 13; Sport und Buch, Köln 2001, p35-42. www.lrz-muenchen.de/~tc131ac/webserver/webdata/index.html

SLIDE 19:

The figure shows the physiological pathway of red blood cell proliferation and points of pharmacological interruption. The pathway of red cell formation starts by the kidney comes to the bone marrow and ends by the muscles. The pharmacological interruptions aim to stimulate the endogenous erythropoietin production. Erythropoietin abuse leads to an increased erythropoeisis in the bone marrow with an increased count of red blood cells. A physiological and legal stimulation is induced by exercise and hypoxia.

Original Abstract of Elliot S (2008): British Journal of Pharmacology, 529–541:

Erythropoiesis-stimulating agents and other methods to enhance oxygen transport

Oxygen is essential for life, and the body has developed an exquisite method to collect oxygen in the lungs and transport it to the tissues. Hb contained within red blood cells (RBCs), is the key oxygen-carrying component in blood, and levels of RBCs are tightly controlled according to the demand for oxygen. The availability of oxygen plays a critical role in athletic performance, and agents that enhance oxygen delivery to tissues increase aerobic power. Early methods to increase oxygen delivery included training at altitude, and later, transfusion of packed RBCs. A breakthrough in understanding how RBC formation is controlled included the discovery of erythropoietin (Epo) and cloning of the *EPO* gene. Cloning of the *EPO* gene was followed by commercial development of recombinant human Epo (rHuEpo). Legitimate use of this and other agents that affect oxygen delivery is important in the treatment of anaemia (low Hb levels) in patients with chronic kidney disease or in cancer patients with chemotherapy-induced anaemia. However, competitive sports was affected by illicit use of rHuEpo to enhance endurance performance. Testing methods for these agents resulted in a cat-and-mouse game, with testing labs attempting to detect the use of a drug or blood product to improve athletic performance (doping) and certain athletes developing methods to use the agents without being detected. This article examines the current methods to enhance aerobic performance and the methods to detect illicit use.

Picture shows: The whole organic systems and possibilities of the O_2-transportation in the body and methods to enhance this oxygen transport.

SLIDE 20:

Clinical examination of the skin may provide evidence of anabolic androgenic steroid abuse. Especially long term abuse of steroids like anabolic androgenic steroids or glucocorticosteroids can lead to striae distensae and/or acne. Other visible side effects can be androgenic alopecia and hypertrichosis, though both are less common. Glucocorticosteroids show tissue atrophy, inhibition of wound recovery and skin weakness. Further biomedical side effects are quite diverse. Stimulants, narcotics, corticotropin, erythropoietin and alcohol are substances that are less often abused and therefore their side effects on the skin are seldom reported. Dehydration can be found as a result of abuse of stimulants (especially amphetamines). Urticaria, erythema and pruritus can result from narcotic abuse. General allergic reactions are sometimes observed in response to abuse of corticotrophin and local allergic reactions (e.g. around the injection area) can be expected by erythropoietin abuse. Alcohol can induce a premature aging in the skin.

SLIDE 21:

The abuse of anabolic androgenic steroids by athletes doing weight-lifting shows an increased rate of striae distensae. Here an atrophy of the skin is observed, mostly in stressed areas of the body, like the shoulder, back, chest and the upper limb. Exercise-induced distension seems to be causable.

The pictures show two examples of striae distensae developed by extensive weight lifting and anabolic androgenic steroid abuse.

Upper picture shows: Striae distensae by extensive weight lifting

Lower picture shows: Striae distensae in a bodybuilder

More detailed information can be found:

Karamfilov & Elsner (2002): Sport als Risikofaktor und therapeutisches Prinzip in der Dermatologie; Hautarzt, 53: 98-103

Wollina, Pabst, Schönlebe, Abdel-Naser, Konrad, Gruner, HAroske, Klemm & Schreiber (2007): Side effect of topical androgenic and anabolic substances and steroids. A short review. Acta Dermatoven APA, 16 (3): 117-122

SLIDE 22:

Young and strong athletes showing acne on their back and/or chest should alarm the physicians. It could be the so-called “steroid-acne” induced by an abuse of anabolic androgenic steroids. The steroids stimulate the sebaceous glands which lead to an increased sebum excretion, increased skin surface lipids and the increase of Propionibacterium acnes.

Original Abstract of Melnik et al. (2007): J Dtsch Dermatol Ges. 5(2), 110-117:

Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem

Abuse of anabolic-androgenic steroids (AAS) by members of fitness centers and others in Germany has reached alarming dimensions. The health care system provides the illegal AAS to 48.1 % of abusers. Physicians are involved in illegal prescription of AAS and monitoring of 32.1 % of AAS abusers. Besides health-threatening cardiovascular, hepatotoxic and psychiatric long-term side effects of AAS, acne occurs in about 50 % of AAS abusers and is an important clinical indicator of AAS abuse, especially in young men 18-26 years of age. Both acne conglobata and acne fulminans can be induced by AAS abuse. The dermatologist should recognize bodybuilding acne, address the AAS abuse, and warn the patient about other potential health hazards.

Upper picture shows: Acne papulopustulosa induced by anabolic-androgenic steroids

Lower picture shows: Acne conglobata induced by anabolic-androgenic steroids

SLIDE 23:

The liver is the most important organ for metabolism and detoxication. The liver is a highly perfused organ, and its cells are arranged to have close contact with the bloodstream. During metabolic processes the liver produces bile, which is important for fat digestion. The main types of the liver cells are the parenchyma cells of the metabolic tissue, the stromal cells as supporting connective tissue, and the so-called Kupffer cells for phagocytosing extraneous particles. Most drugs are metabolised by the liver, consequently biomedical side effects affect the liver tissue. Especially anabolic androgenic steroids can lead to biliary stasis, cholestasis, peliosis hepatis, hepatoma and dysregulation of lipoproteins. Hormones and related substances influence general organ growth and functional disturbances. An acute liver failure and hepatitis can be consequences of stimulants. Narcotics, alcohol and beta-blocker can lead to acute liver failure, fatty liver (steatosis hepatis) and cirrhosis furthermore there are quite unspecific symptoms of upper abdominal disturbances.

More detailed information can be found:

Müller-Platz, Nishino & Sarikaya (2007): Gastrointestinal tract and liver. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p66-88. www.doping-prevention.com

SLIDE 24:

Liver function disturbances and diseases due to anabolic androgenic steroids treatment are mainly based on the administration of 17-α-alkylated steroids (e.g. methyltestosterone, stanozolol, oxymetholone, fluoxymesterone, norethandrolone and metandienone). Possible liver disorders are e.g. biliary stasis, cholestatsis, peliosis hepatis and hepatomas. Furthermore, investigations reported a lowering of high-density lipoprotein (the "good" one), an increasing of low-density lipoprotein (the "bad" one) and atherogenic-promoting apolipoprotein A. These side effects are usually reversible upon discontinuation.

Picture shows: Inflammations of the liver; fatty degeneration of the tissue and the formation of liver cysts are examples of the direct damage to tissue that may occur.

Original Abstract of Hartgens & Kuipers (2004): Sports Med 34 (8), p513-554:

Effects of Androgenic-Anabolic Steroids in Athletes

Androgenic-anabolic steroids (AAS) are synthetic derivatives of the male hormone testosterone. They can exert strong effects on the human body that may be beneficial for athletic performance. A review of the literature revealed that most laboratory studies did not investigate the actual doses of AAS currently abused in the field. Therefore, those studies may not reflect the actual (adverse) effects of steroids. The available scientific literature describes that short-term administration of these drugs by athletes can increase strength and bodyweight. Strength gains of about 5–20% of the initial strength and increments of 2–5kg bodyweight that may be attributed to an increase of the lean body mass have been observed. A reduction of fat mass does not seem to occur. Although AAS administration may affect erythropoiesis and blood haemoglobin concentrations, no effect on endurance performance was observed. Little data about the effects of AAS on metabolic responses during exercise training and recovery are available and, therefore, do not allow firm conclusions. The main untoward effects of short- and long-term AAS abuse that male athletes most often self-report are an increase in sexual drive, the occurrence of acne vulgaris, increased body hair and increment of aggressive behaviour. AAS administration will disturb the regular endogenous production of testosterone and gonadotrophins that may persist for months after drug withdrawal. Cardiovascular risk factors may undergo deleterious alterations, including elevation of blood pressure and depression of serum high-density lipoprotein (HDL)-, HDL2- and HDL3-

cholesterol levels. In echocardiographic studies in male athletes, AAS did not seem to affect cardiac structure and function, although in animal studies these drugs have been observed to exert hazardous effects on heart structure and function. In studies of athletes, AAS were not found to damage the liver. Psyche and behaviour seem to be strongly affected by AAS. Generally, AAS seem to induce increments of aggression and hostility. Mood disturbances (e.g. depression, [hypo-]mania, psychotic features) are likely to be dose and drug dependent. AAS dependence or withdrawal effects (such as depression) seem to occur only in a small number of AAS users. Dissatisfaction with the body and low self-esteem may lead to the so-called 'reverse anorexia syndrome' that predisposes to the start of AAS use. Many other adverse effects have been associated with AAS misuse, including disturbance of endocrine and immune function, alterations of sebaceous system and skin, changes of haemostatic system and urogenital tract. One has to keep in mind that the scientific data may underestimate the actual untoward effects because of the relatively low doses administered in those studies, since they do not approximate doses used by illicit steroid users. The mechanism of action of AAS may differ between compounds because of variations in the steroid molecule and affinity to androgen receptors. Several pathways of action have been recognised. The enzyme 5-α-reductase seems to play an important role by converting AAS into dihydrotestosterone (androstanolone) that acts in the cell nucleus of target organs, such as male accessory glands, skin and prostate. Other mechanisms comprises mediation by the enzyme aromatase that converts AAS in female sex hormones (estradiol and estrone), antagonistic action to estrogens and a competitive antagonism to the glucocorticoid receptors. Furthermore, AAS stimulate erythropoietin synthesis and red cell production as well as bone formation but counteract bone breakdown. The effects on the cardiovascular system are proposed to be mediated by the occurrence of AAS-induced atherosclerosis (due to unfavourable influence on serum lipids and lipoproteins), thrombosis, vasospasm or direct injury to vessel walls, or may be ascribed to a combination of the different mechanisms. AAS-induced increment of muscle tissue can be attributed to hypertrophy and the formation of new muscle fibres, in which key roles are played by satellite cell number and ultrastructure, androgen receptors and myonuclei.

SLIDE 25:

The musculoskeletal system is strongly affected by several prohibited substances. Anabolic androgenic steroids may cause bone fractures, tendon pathology and rhabdomyolysis or a premature closure of the epiphysis resulting in growth retardation. Furthermore the steroids may cause changes in the tendon structure itself. Accordingly, spontaneous tendon ruptures of young athletes with an adequate

muscle status should warn the physician to think about anabolic androgenic steroid abuse.

Hormones and related substances may result in clinical symptoms like acromegaly by an oversecretion in the pituitary gland. The visible changes of bone and cartilage are amongst others the enlargement of hands and feet, nose, chin, teeth, tongue and ears.

Beta-2-agonists are used for medical treatment of asthmatic attacks. They influence several metabolic and physiological processes in the skeletal muscle. Negative effects on the bone architecture like decreased bone mass and decreased bone mineral density are followed by muscle tremor and muscle cramps.

Glucocorticosteroids can lead to osteoporosis and an increased risk of fractures and a delayed bone repair up to a decrease in muscle nutrition and a severe risk of muscle atrophy.

Beta-blockers are medically used in the treatment of cardiovascular diseases, but show adverse effects on the skeletal muscle, including a reduced glycogenolysis.

More detailed information can be found:

Müller-Platz, Nishino & Sarikaya (2007): Gastrointestinal tract and liver. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p66-88. www.doping-prevention.com

SLIDE 26:

The biomedical side effects of anabolic androgenic steroids show different changes in the musculoskeletal system. There are reports about bone fractures and a premature closure of the epiphysis resulting in growth retardation. Furthermore, the steroids can cause changes in the tendon structure itself. Anabolic steroids appear to induce reversible changes in the biomechanical properties of tendons producing a stiff, less elastic tendon. It is possible that the rapid strength adaptations being produced by anabolic androgenic steroids in skeletal muscle are not simultaneously accompanied by slower adapting, less vascular tendon structures, making tendons the weakest link in the chain. Muscular destruction by rhabdomyolysis may occur after intake of anabolic androgenic steroids in combination with weight-training programmes.

A case report about multiple tendon ruptures by an athlete (football) abusing anabolics.

Original Abstract of Isenberg et al. (2008): Unfallchirurg, 46-49:**Successive ruptures of patellar and Achilles tendons. Anabolic steroids in competitive sports**

Derivatives of testosterone or of 19-nor-testosterone are used as anabolics for the purpose of improving performance although the effect of anabolics is known still to be under discussion. The use of anabolic steroids continues among competitive athletes despite increased controls and increasingly frequent dramatic incidents connected with them. Whereas metabolic dysfunction during anabolic use is well documented, ruptures of the large tendons are rarely reported. Within 18 months, a 29-year-old professional footballer needed surgery for rupture of the patellar tendon and of both Achilles tendons. Carefully directed questioning elicited confirmation that he had taken different anabolic steroids regularly for 3 years with the intention of improving his strength. After each operation anabolic steroids were taken again at a high dosage during early convalescence and training. Minimally invasive surgery and open suturing techniques led to complete union of the Achilles tendons in good time. Training and anabolic use started early after suturing of the patellar tendon including bone tunnels culminated in histological confirmed re-rupture after 8 weeks. After a ligament reconstruction with a semitendinosus tendon graft with subsequent infection, the tendon and reserve traction apparatus were lost. Repeated warnings of impaired healing if anabolic use was continued had been given without success. In view of the high number of unrecorded cases in competitive and athletic sports, we can assume that the use of anabolic steroids is also of quantitative relevance in the operative treatment of tendon ruptures.

Picture shows: The patella (yellow arrows) and their lost connection to the tibia (rupture of the patellar tendon).

SLIDE 27:

The endocrine organs are affected in different ways by prohibited substances. Anabolic androgenic agents influence the reproductive system of the female and male. Furthermore, the insulin resistance and glucose tolerance are influenced by steroids. The thyroid function is affected by growth hormones and gonadotrophins, whereas glucocorticosteroids affect the adrenal cortex.

More detailed information can be found:

Georgieva (2007): Reproductive and endocrine system. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p89-111. www.doping-prevention.com

SLIDE 28:

Anabolic androgenic steroids affect the male reproductive system. The secretory and gametogenic functions of the testis are both dependent upon the secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, which stimulates the secretion of the anterior pituitary gonadotrophins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). As derivatives of testosterone, AAS have pronounced effects on the male hypothalamic-pituitary-gonadal axis and their abuse can result in the clinical syndrome of hypogonadotrophic hypogonadism. This steroid-induced hypogonadal state is characterized by decreased serum concentrations of FSH and LH, low endogenous testosterone production, impaired spermatogenesis and testicular atrophy. These effects stem from the negative feedback of anabolic steroids on the hypothalamic-pituitary axis and possibly from the local suppressive effects of excess androgens on the testes:
The administration of AAS mimics an enhanced level of circulating endogenous testosterone. High testosterone levels, as well as AAS, inhibit LH secretion by acting directly on the anterior pituitary gland and by inhibiting the secretion of GnRH from the hypothalamus. This in turn causes a corresponding decrease in secretion of both LH and FSH and the decrease in LH reduces the production of endogenous testosterone. Administration of high doses of testosterone induces supraphysiological levels of serum total and free testosterone. Serum concentrations of estradiol, androstenedione and Dihydrotestosterone (DHT) also increase because of peripheral conversion of AAS.

Picture shows: Comparison of a normal-size testis to a decreased testis after anabolic androgenic steroids abuse.

More detailed information can be found:

Georgieva (2007): Reproductive and endocrine system. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p89-111. www.doping-prevention.com

SLIDE 29:

Insulin resistance and a reduced glucose level can be induced by anabolic androgenic steroid abuse. These changes mimic type 2-diabetes and are observed in patients treated with 17-alkylated oral androgens and in male athletes using AAS over a long period of time (3-7 years). Although there has been no documented diabetes mellitus in athletes using anabolic steroids, these changes are associated with increased cardiovascular risk.

More detailed information can be found:

Georgieva (2007): Reproductive and endocrine system. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p89-111. www.doping-prevention.com

SLIDE 30:

Anabolic androgenic steroids lead to an imbalance between free estrogen and free androgen actions in the male breast tissue. As a consequence gynaecomastia can occur.

Both pictures show: Gynaecomastia in a 30-year-old amateur Bodybuilder (upper picture) and gynaecomastia in a 25-year-old professional bodybuilder (lower picture).

SLIDE 31:

The female endocrine system is affected by anabolic androgenic steroid (AAS) abuse. AAS intake suppresses the hypothalamic-pituitary-gonadal axis, which regulates parts of the immune and reproductive systems. Furthermore, serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, sex hormone-binding globulin (SHBG) are decreased and serum levels of testosterone are elevated. This imbalance of the endocrine system may lead to an enlargement of the clitoris, an atrophy of the breast, an abnormal hair growth (male pattern of body hair). All these effects are normally irreversible. Clinical consequences are possible:

- virilisation (appearance of secondary sex characteristics of the male in a female),
- hirsutism (excessive growth of hair with abnormal distribution) and
- amenorrhea (absence of the menstrual cycle).

More detailed information can be found:

Georgieva (2007): Reproductive and endocrine system. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 007, p89-111. www.doping-prevention.com

SLIDE 32:

The central nervous system is mainly affected by anabolic androgenic steroids, beta-2-agonists, narcotics and stimulants. AAS abuse can be expressed by increased levels of irritability, aggression, personal disturbances and psychiatric diagnosis.

Activation of the sympathetic nervous system is associated with the release of adrenaline and noradrenaline. Narcotics are associated with pain relief and mood alterations in wide range from sleep and total immobilization of the body up to euphoria and over-excitation. Sympathomimetics like stimulants are drugs activating the central nervous system by catecholamine (e.g. adrenaline and noradrenaline) actions.

More detailed information can be found:

Grucza (2007): Psychological effects and addiction including CNS. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p135-153. www.doping-prevention.com

SLIDE 33:

Abuse of prohibited substances can lead to changes of the central nervous system e.g. dependencies. A physical dependency becomes evident when the body is deprived of drugs. Such deprivation leads to physical symptoms that vary with the drug and may include: pain (opiates), severe tremors (alcohol) and convulsions (barbiturates and benzodiazepines). Psychological dependency can last far longer than physical dependency. It is based more on the individual's traits than on the substance itself: habits, affective states and lifestyle. Reward systems play an important role in the development of psychological dependence. Cocaine and amphetamines are good examples of substances with high psychological and low physical dependency.

More detailed information can be found:

Grucza (2007): Psychological effects and addiction including CNS. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p135-153. www.doping-prevention.com

SLIDE 34:

Gene technology:

The definition of gene doping is based on the specific modulation of the genetic information and the expression of genes. To study, identify or modify the genes of living organisms, bio- and gene technology is used, a term that refers to a whole range of tools and techniques. This includes also techniques to transfer genetic material like DNA or RNA in order to supply possible absent components or to compensate for abnormal genes. Further techniques are the sequencing of the DNA,

cloning technology, gene marker technology, transgenic techniques, and gene silencing or gene therapy. All these techniques are used by many scientists, including (molecular-)biologists, (bio-)chemists, geneticists and medical doctors. In the general public, gene doping is strictly associated with gene therapy, but it is more, it is the consequent appliance of gene technology. This runs from the use of specific antibodies to modify (stimulate or inhibit) gene expression to a selective modification of a cell, a gene or the modulation of a receptor, to the specific regulation of gene expression after gene transfer. Therefore, strategies to detect gene doping must have more than one focus: on the one hand it has to detect if a performance enhancement gene itself or a gene modulating construct is transferred into the body and on the other hand, if important target genes for physical performance were switched on or off with special substances.

More detailed information can be found:

Schulz (2007): Gene doping. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p186-208. www.doping-prevention.com

SLIDE 35:

The 2008 Prohibited List defines gene doping as *"the non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to enhance athletic performance".*

The idea of gene therapy is to implement the modified genes into the cell by the help of specific transporters. After the implementation the corrected/new functional proteins can be synthesized by the cell and the disease can be healed or at least lowered. The medical purpose of gene therapy is to correct defective genes that are responsible for the disease development, like hereditary diseases. But the problem is the abuse of the therapeutic idea for sport purposes.

If the correction of defective genes is possible, it wouldn't be far to the modification of muscle genes. Possible aims of abuse could be:

1. Endurance genes

Endurance performance is strongly related to optimal tissue oxygenation and allocation of energy. This implicates an enhancement of the oxygen delivering system, e.g. the blood itself or the blood flow or the improvement of hormones regulating and proteins which modulate the energy metabolism. Possibly interesting factors could be erythropoietin (EPO), hypoxia-inducible factors (HIF), and angiotensine converting enzyme (ACE).

2. Muscle performance enhancement

..via hypertrophy, hyperplasia and better regeneration. Performance enhancement in sport is dependent upon adaptations of the skeletal muscle and therefore the remodelling of the myofibres. Responses of the myofibres to training include activation of intracellular signalling pathways and genetic reprogramming via endocrine mechanisms, growth factors and mechanical stimuli which lead to alterations of muscle mass, contractile properties, and metabolic states. Possibly interesting factors could be mechano growth factor (MGF), insulin-like growth factor-1 (IGF-1), growth hormone (GH), myostatin/growth differentiation factor (gdf-8).

More detailed information can be found:

Schulz (2007): Gene doping. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p186-208. www.doping-prevention.com

SLIDE 36:

Endurance genes:

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

More detailed information can be found:

Schulz (2007): Gene doping. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p186-208. www.doping-prevention.com

SLIDE 37:

Muscle performance enhancement via hypertrophy, hyperplasia and better regeneration: Performance enhancement in sport depends upon adaptations of the skeletal muscle and therefore the remodelling of the myofibres. Responses of the myofibres to training include activation of intracellular signalling pathways and genetic reprogramming via endocrine mechanisms, growth factors and mechanical stimuli which lead to alterations of muscle mass, contractile properties, and metabolic

states. Therefore, modulating hormonal status and growth factors is a target for gene therapy for people with degenerative muscle conditions. This includes for example hormones like androgens, growth hormone, insulin or growth factors like MGF, IGF, myostatin (GDF-8), TGF-ß and follistatin. Also influencing factors which block or induce muscle related hormones and growth factors are relevant, e.g. decorin or IL-6 and TNF-α, and therefore candidates for gene doping.

Upper picture shows: Different genes influencing the muscular strength.

Lower picture shows: At 4.5 years of age the child showed increased muscle mass and strength due to an increased genetic myostatin mutation. He could hold two 3-kg dumb-bells in horizontal suspension with extended arms.

More detailed information can be found:

Schulz (2007): Gene doping. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p186-208. www.doping-prevention.com

Schuelke et al. N Engl J Med. 2004 Jun 24; 350(26), p2682-2688.

SLIDE 38:

Original Abstract of Tentori & Graziani (2007): Pharmacol Res, 55(5), 359-69: **Doping with growth hormone/IGF-1, anabolic steroids or erythropoietin: is there a cancer risk?**

Anabolic steroid and peptide hormones or growth factors are utilized to increase the performance of athletes of professional or amateur sports. Despite their well-documented adverse effects, the use of some of these agents has significantly grown and has been extended also to non-athletes with the aim to improve appearance or to counteract ageing. Pre-clinical studies and epidemiological observations in patients with an excess of hormone production or in patients chronically treated with hormones/growth factors for various pathologies have warned about the potential risk of cancer development and progression which may be also associated to the use of certain doping agents. Anabolic steroids have been described to provoke liver tumours; growth hormone or high levels of its mediator insulin-like growth factor-1 (IGF-1) have been associated with colon, breast, and prostate cancers. Actually, IGF-1 promotes cell cycle progression and inhibits apoptosis either by triggering other growth factors or by interacting with pathways which have an established role in carcinogenesis and cancer promotion. More recently, the finding that erythropoietin (Epo) may promote angiogenesis and inhibit apoptosis or modulate chemo- or radiosensitivity in cancer cells expressing the Epo receptor, raised the concern that the use of recombinant Epo to increase tissue oxygenation might favour tumour

survival and aggressiveness. Cancer risk associated to doping might be higher than that of patients using hormones/growth factors as replacement therapy, since enormous doses are taken by the athletes often for a long period of time. Moreover, these substances are often used in combination with other licit or illicit drugs and this renders almost unpredictable all the possible adverse effects including cancer. Anyway, athletes should be made aware that long-term treatment with doping agents might increase the risk of developing cancer.

SLIDE 39:

Several biomedical side effects of the abuse of prohibited substances are expressed in the immune system. These biomedical side effects depend on the type of the consumed drug, as well as on the amount and duration of intake and the sensitivity of the body. There is a large inter-individual variability in responses to a drug. Usually the doses used in sports are much higher than those tested in clinical trials and used for therapeutic purposes. The abuse of several drugs in combination is frequent, leading to a higher risk of side effects.

Immunological side effects induced by anabolic androgenic steroids, hormones and related substances, beta-2-agonists, stimulants, narcotics, cannabinoids, glucocorticosteroids, alcohol, beta-blockers are:

- Increased production of pro-inflammatory cytokines
- Immunosuppression
- Increased susceptibility to infections
- Increased tumorigenesis
- Immune modulation

More detailed information can be found:

Ortega, Hinchado, Giraldo (2007): Immune system and skin: The importance of studying this problem. In Sarikaya, Peters, Schulz, Schönfelder & Michna: Congress Manual: Biomedical Side Effects of Doping; München 2007, p119-134. www.doping-prevention.com

SLIDE 40:

Nutritional supplements are naturally in the body existing substances that are additionally consumed to normal daily nutrition, like glucose, minerals, vitamins or trace elements. These substances are partly essential for the growth and development of a multicellular organism, like the human body. These supplements mostly consist of several substances. The medical purpose for an additional

substitution of nutritional supplements is a deficiency in the body due to malnutrition or illnesses. The main reasons for the public to use nutritional supplements are to promote health, reduce risk of getting sick and at least control body weight. Most of the supplements are not prohibited within the “List”.

Nutritional supplements could be necessary for **some competitive athletes to perform the intensity and duration of their sports. They have an extremely high calorie usage level that cannot be covered by normal daily nutrition** (like Tour de France, Ultra Triathlon etc.).

Critical substances are some vitamins of the B group in vegetarian athletes.

Nevertheless, a well-balanced nutrition is much better than any nutritional supplementation and of course intake levels have to be taken into account to avoid the effect of an ‘overdosage’.

SLIDE 41:

One of the main risk factors of nutritional supplements can be positive doping testing by contaminated supplements. These **unlabelled** ingredients can lead in the extreme case even to positive doping testing. As a consequence the **biomedical side effects depend on the kind of the “unlabelled” substance**. **Most detected substances are various anabolic-androgenic steroids or stimulants**.

It is a matter of fact that a lot of sportsmen are using supplements without the knowledge of side effects and recommended intake levels. In the face of the great market of nutritional supplements (about 12 billion US$ in the USA in the year 2001) and the tremendous sales worldwide, the edge between recommended use and misuse is floating.

Furthermore, the assumption that the use of nutritional supplements can be used to prevent possible nutritional deficiencies may lead to less attention concerning a healthy, well-balanced diet.

Table shows: An International Olympic Committee analysis of 600 over-the-counter nutritional supplements found that one seventh of the investigated supplements contained banned substances such as anabolic steroids.